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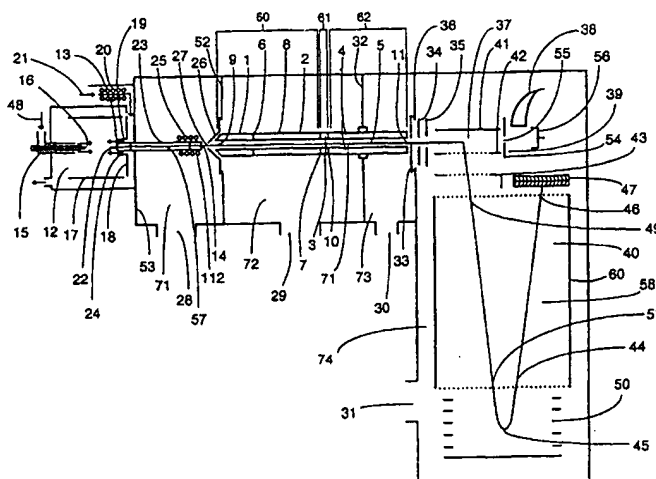
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(54) Title: MASS SPECTROMETRY WITH MULTIPOLE ION GUIDES



## (57) Abstract

A mass spectrometer (40) is configured with individual multipole ion guides (60, 62) configured in an assembly in alignment along a common centerline (5) wherein at least a portion of each multiple ion guide (60, 62) mounted in the assembly resides in a vacuum region (72, 73) with higher background pressure. Said multiple ion guides (60, 62) configured in a higher pressure vacuum region (72, 73) are operated in mass to charge selection and ion fragmentation modes. Individual sets of RF, +/- DC and resonant frequency waveform voltage supplies provide potentials to the rods of each multiple ion guide allowing the operation of ion transmission, ion trapping, mass to charge selection and ion fragmentation functions independently in each ion guide (60, 62). The presence of background pressure maintained sufficiently high to cause ion to neutral gas collisions along a portion of each multiple ion guide linear assembly allows the conducting of Collisional Induced Dissociation (CID) fragmentation of ions by axially accelerating ions from one multiple ion guide into an adjacent ion guide, analogous to a triple quadrupole ion function.

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## Mass Spectrometry with Multipole Ion Guides

### Related Applications

The present application claims the priority of U.S. Patent Application No. 09/235,946 filed January 22, 1999, and PCT Application No. PCT/US99/01335, filed January 22, 1999, both of which claim the priority of U.S. Provisional Application Serial No. 60/072,374 filed January 23, 1998, and U.S. Provisional Application No. 60/087,246, filed May 29, 1998. The priority of all of these prior applications is claimed, the disclosures of which are fully incorporated herein by reference.

### Field of Invention

This invention relates to the field of mass spectrometric analysis of chemical species. More particularly it relates to the configuration and operation use of multiple multipole ion guide assemblies operated in higher pressure vacuum regions.

### Background of the Invention.

Mass Spectrometers (MS), have been used to solve an array of analytical problems involving solid, gas and liquid phase samples with both on-line and off-line techniques. Gas Chromatography (GC), Liquid Chromatography (LC), Capillary Electrophoresis (CE) and other solution sample separation systems have been interfaced on-line to mass spectrometers configured with a variety of ion source types. Some ion source types operate at or near atmospheric pressure and other ion source types produce ions in vacuum. Mass spectrometers operate in vacuum with different mass analyzer types requiring different vacuum background pressure for optimal performance. The present invention comprises a configuration of one or more multipole ion guides configured in a mass spectrometer. Although the invention can be applied to multipole ion guides comprising any number of poles, the description of the invention given below will apply primarily to to quadrupole or four pole ion guide assemblies. Higher mass to charge separation resolution can be achieved with quadrupole ion guides when compared with the performance of ion guides configured with more than four poles. Mass to charge selective resonant frequency excitation can also be more readily applied with quadrupoles than with ion guides having higher numbers of poles. Quadrupole ion guides have been configured as the primary elements in single and triple quadrupole mass analyzers and as part of hybrid mass spectrometers that include Time-Of-Flight, Magnetic Sector, Fourier Transform and three dimensional quadrupole ion trap mass analyzers. Conventionally, quadrupole ion guides operated as mass to charge filters, are configured in background vacuum pressures that minimize or eliminate ion to neutral background gas collisions. A wider range of background pressures have been used when operating quadrupoles in non mass to charge selection RF only ion transmission mode. In some mass spectrometer instruments, quadrupole ion guides operated in RF only ion transmission mode are configured in a region where the background vacuum pressure is maintained sufficiently

high to promote collisional damping of ion kinetic energy or Collisional Induced Dissociation (CID) fragmentation of ions traversing the ion guide length.

Conventionally, quadrupole mass analyzers with electron multiplier or photomultiplier detectors are operated in analytical mass to charge selection mode with background pressures typically maintained below  $2 \times 10^{-4}$  torr range. However, operation of multipole ion guides at elevated background vacuum pressures with ion mass to charge separation have been described. Ferran in U.S. Patent Numbers 5,401,962 and 5,613,294, which are fully incorporated herein by reference, describes a small quadrupole array with an electron ionization (EI) ion source and a faraday cup detector operated as a low mass to charge range gas analyzer. This small quadrupole array can be operated in background vacuum pressures as high as  $1 \times 10^{-2}$  torr. Performance of this short quadrupole array begins to decrease when the background pressure increases to the point where the mean free path of an ion is shorter than the quadrupole rod length. Douglas in U.S. Patent Number 5,179,278 describes a quadrupole ion guide configured to transmit ions from an Atmospheric Pressure Ionization (API) source into a three dimensional quadrupole ion trap. The quadrupole ion guide described by Douglas in Patent Number 5,179,278, which is fully incorporated herein by reference, can be operated as a trap to hold ions before releasing the trapped ions into the three dimensional quadrupole ion trap. During ion trapping, the potentials applied to the rods or poles of this quadrupole ion guide can be set to limit the range of ion mass to charge values released to the ion trap. The quadrupole ion guide can also be operated with resonant frequency excitation collisional induced dissociation fragmentation of trapped ions prior to introducing the trapped fragment ions into the three dimensional ion trap. After the quadrupole ion guide has released its trapped ions to the three dimensional ion trap, it is refilled during the three dimensional ion trap mass analysis time period. A multipole ion guide that extends continuously through multiple vacuum pumping stages is described by Whitehouse et. al. in U.S. Patent Number 5,652,427, which is fully incorporated herein by reference. A portion of the multipole ion guide length is positioned in a vacuum region with background pressures greater than one millitorr insuring ion to neutral gas background collisions. Dresch et. al. in U.S. Patent Number 5,689,111, which is fully incorporated herein by reference, describe a hybrid multipole ion guide Time-Of-Flight (TOF) mass spectrometer wherein the multipole ion guide is configured and operated to trap ions and release a portion of the trapped ions into the pulsing region of the TOF mass analyzer. Whitehouse et. al. in U.S. Patent Application Serial Number 08/694,542, which is fully incorporated herein by reference, describe a hybrid mass spectrometer wherein at least one multipole ion guide is configured with a Time-Of-Flight mass analyzer. As described, at least one quadrupole ion guide can be operated in ion transmission, ion trapping, mass to charge selection and/or CID fragmentation modes or combinations thereof coupled with Time-Of-Flight mass to charge analysis. The hybrid quadrupole Time-Of-Flight apparatus and method described, allows a range of  $MS/MS^n$  mass analysis functions to be performed. In an improvement over the prior art, one embodiment of the present invention comprises multiple quadrupole ion guides configured and operated in a higher pressure vacuum region of a hybrid TOF mass analyzer improving the mass analyzer  $MS/MS^n$  performance and extending the analytical capability of a hybrid TOF mass analyzer.

Multipole ion guides operated in RF only mode at elevated pressures have been used as an effective means to achieve damping of ion kinetic energy during ion transmission from

Atmospheric Pressure Sources to mass analyzers. A quadrupole ion guide, operated in RF only mode in background pressures greater than  $10^{-4}$  torr, configured to transport ions from an API source to a quadrupole mass analyzer is described by Douglas et. al. in U.S. patent 4,963,736, which is fully incorporated herein by reference. Ion collisions with the neutral background gas serve to damp the ion kinetic energy during ion transmission through the ion guide. The ion collisions with the neutral background gas reduces the primary ion beam kinetic energy spread and improves ion transmission efficiency through the ion guide and downstream of the ion guide. Multipole ion guides operated in elevated background pressures have been used as collision cells for the CID fragmentation of ions in triple quadrupoles, hybrid magnetic sector and TOF mass analyzers. Multipole ion guides configured as collision cells are operated in RF only mode with a variable DC offset potential applied to all rods. Thomson et. al. in U.S. Patent Number 5,847,386, which is fully incorporated herein by reference, describe a multipole ion guide assembly configured to create a DC electric field along the ion guide axis to move ions axially through a collision cell or to promote CID fragmentation within a collision cell by oscillating ions axially back and forth along the ion guide assembly length. As described, the ion guide assembly with an axial field is operated in RF only mode with a common RF applied to all poles of the quadrupole ion guide assembly. Multipole ion guide collision cells that have been incorporated in commercially available mass analyzers and that have been described in the literature are configured as individual ion guide assemblies with a common RF applied along the collision cell multipole ion guide length. French in U.S. Patent Number 4,328,420, which is fully incorporated herein by reference, describe multipole ion guides configured with open structure rod assemblies. These open structure rod assemblies operated in RF only mode, are configured as collision cells in triple quadrupoles and as a means to reduce the gas pressure in analytical quadrupoles when interfaced to corona discharge atmospheric pressure ion sources. French describes operating all mass filter analytical quadrupoles in conventional manner with low vacuum background pressures. In the present invention, at least a portion of the length of quadrupole ion guides operating in mass to charge selection mode are configured in a higher background pressure vacuum region where collisions between ions and neutrals can occur. This configuration of the invention allows increased performance capabilities and reduced instrument cost as is described in the following sections.

The collision cell multipole ion guide configured in triple quadrupole mass analyzers is typically surrounded by an enclosure to maintain locally higher pressure in the collision cell multipole ion guide. The enclosure surrounding the collision cell multipole ion guide is generally located in a lower pressure vacuum region, is configured to minimize the transfer of higher pressure collision cell background gas into the surrounding lower vacuum pressure chamber. Commercially available triple quadrupoles, shown as prior art in Figure 20 generally are configured with three multipole ion guides in one vacuum pumping stage. The elevated pressure within the collision cell is maintained by leaking collision gas into the enclosure surrounding the collision cell multipole ion guide. Gas leaks out of the collision cell through the enclosure entrance and exit apertures configured along the triple quadrupole centerline. One aspect of the present invention is the configuration of multiple quadrupole ion guides positioned in a common region of higher vacuum pressure configured so that individual quadrupoles can be operated in ion mass to charge selection and/of CID fragmentation modes. A further aspect of the invention is the configuration of multiple quadrupole ion guides in a vacuum region of elevated background vacuum pressure wherein

each quadrupole can be operated in mass to charge selection and/or ion fragmentation modes to achieve MS/MS<sup>n</sup> mass analysis functions.

Conventional triple quadrupole mass analyzers interfaced to API sources are configured with sufficient vacuum pumping speed in the mass analyzer vacuum region to maintain a vacuum level that prevents or minimizes ion collisions with the background gas. The low pressure vacuum is maintained even with limited gas leaks into the chamber from a collision cell and an ion source. Vacuum pressure in a triple quadrupole collision cell enclosure is generally maintained at 0.5 to 8 millitorr and the surrounding analyzer vacuum chamber pressure is maintained in the low  $10^{-5}$  to  $10^{-6}$  torr range. A diagram of the multipole ion guide configuration of a conventional triple quadrupole mass analyzer 550 interfaced to Atmospheric Pressure Ion source 560 is shown in Figure 20. Individual multipole ion guide assemblies 558, 554, 555 and 556 are aligned along the same centerline axis in a three stage vacuum pumping system. Capillary 564 provides a leak from atmospheric pressure Electrospray ion source 560 into first vacuum pumping stage 551. Ions produced in Electrospray source 560 are transferred into vacuum through a supersonic free jet expansion formed on the vacuum side of capillary exit 561. A portion of the ions introduced into vacuum continue through the orifice in skimmer 559, multipole ion guide 558, the orifice in electrode 561, multipole ion guide 554, the orifice in electrode 566, multipole ion guide 555, the orifice in electrode 567, multipole ion guide 556, the orifice in electrode 568 to detector 565. The pressures in vacuum stages 551, 552 and 553 are typically maintained at .5 to 4 torr, 1 to 8 millitorr and  $<1 \times 10^{-5}$  torr respectively while the pressure inside collision cell 557 is maintained at 0.5 to 8 millitorr. Triple quadrupoles are configured to perform MS or a single MS/MS sequence mass analysis functions. In an MS/MS experiment, ions produced at or near atmospheric pressure, are transported through multiple vacuum stages to the low pressure vacuum region 553 where mass to charge selection occurs in quadrupole 554 with little or no ion to neutral collisions. Mass to charge selected ions are then accelerated into a region of elevated pressure in collision cell multipole ion guide 555. The resulting fragment ion population are directed into quadrupole 556 residing in low pressure vacuum region 553. Mass to charge selection is conducted on the ion population traversing quadrupole 556 with few or no ion to neutral collisions prior to detection of stable trajectory ions exiting quadrupole 556 by ion detector 565. Quadrupole 554 is configured with RF only sections 562 and 568 at its entrance and exit ends respectively. Quadrupole 556 is also shown with RF only sections at its entrance and exit end. In commercially available hybrid quadrupole TOF mass analyzers quadrupole 556 is replaced by a TOF mass analyzer residing in a fourth vacuum pumping stage. Such conventional triple quadrupoles and hybrid quadrupole TOF mass analyzers can conduct only MS and MS/MS mass analysis functions with axial DC acceleration CID ion fragmentation. Mass to charge selection is conducted in the quadrupoles by operating the near the tip of the first stability region by applying the appropriate RF and DC potentials to the quadrupole rods. The present inventions, described below, allow the ability to conduct MS, MS/MS and MS/MS<sup>n</sup> mass analysis functions with single or multiple axial DC acceleration CID ion fragmentation or resonant frequency excitation CID ion fragmentation. Single or multiple value quadrupole mass to charge selection in the present invention can be achieved using resonant frequency ion ejection applied to the quadrupole rods, by applying RF and DC potentials to the quadrupole rods or combinations of both.

As diagrammed in Figure 20, a collision cell of a conventional triple quadrupole is configured inside vacuum chamber 553. The placement of a multipole ion guide collision cell inside a vacuum chamber maintained a pressures less than  $10^{-5}$  torr requires that the pumping speed evacuating vacuum chamber 553 be sufficient to remove the gas load leaking from collision cell 557. This added vacuum pumping burden increases the cost and complexity of an API MS/MS mass analyzer. One aspect of the invention is the configuration of multiple quadrupole ion guides in a higher pressure vacuum region of an API source using the background pressure formed by the gas leak from atmospheric pressure to perform CID ion fragmentation. Mass to charge selection and CID ion fragmentation is performed in the first or second vacuum stage of an Atmospheric Pressure Ion Source mass analyzer, eliminating the need for a separate collision cell with its additional gas loading on the vacuum system. The configuration of multiple quadrupoles in the higher pressure region of the first or second vacuum stage of API quadrupole and hybrid mass analyzers reduces the system vacuum pumping speed requirements and its associated costs. Another aspect of the invention is the configuration of multiple quadrupole ion guides that have pole dimensions considerably reduced in size from quadrupole assemblies typically found in commercially available triple quadrupoles or hybrid quadrupole TOF mass analyzers. The reduced quadrupole rod or pole diameters, cross center rod spacing ( $r_0$ ) and length minimizes the ion transmission time along each quadrupole assembly axis. This increases the analytical speed of the mass spectrometer for a range of mass analysis functions. The reduced quadrupole size require less space and power to operate, decreasing system size and cost without decreasing performance. Another aspect of the invention is the configuration of a multipole ion guide that extends continuously into multiple vacuum stages into the multiple quadrupole assembly positioned over at least a portion of its length in the higher pressure region of an API MS instrument. Multiple vacuum pumping stage ion guides are described by Whitehouse et. al. in U.S. Patent Number 5,652,427. As will be described below, configuring a multiple vacuum stage quadrupole ion guide with additional quadrupole ion guides in a linear assembly allows enables the performing of a wide range of mass analysis functions with a single mass analyzer instrument.

Quadrupole ion guides as described by Brubaker in U.S. Patent 3,410,997, Thomson et. al. in U.S. Patent 5,847,386 and Ijames, Proceedings of the 44th ASMS Conference on Mass Spectrometry and Allied Topics, 1996, p 795, which are fully incorporated herein by reference, have been configured with segments or sections where RF voltage generated from a single RF supply is applied to all segments of the ion guide assembly or rod set. Ijames describes operating the quadrupole assembly in RF only ion transport and trapping mode. Typically, as described by Brubaker, an AC or RF only entrance and exit segment will be configured in a quadrupole rod set to minimize fringing field effects for ions entering or leaving the quadrupole. The RF voltage is typically applied to the entrance and exit quadrupole sections through capacitive coupling with the primary RF supplied to the central rod section or segment. Offset potentials, that is the common DC voltage applied to all four poles of a given quadrupole segment, can be set independently for each segment to accelerate ions from one ion guide segment to the next within the quadrupole ion guide assembly. The offset potential applied to segments of an ion guide can be set to trap ions within an ion guide section or segment as well. In the following discussions, a quadrupole or multipole ion guide assembly may include segments or sections but all RF voltage applied to each rod of each segment originates from a common RF supply. In one aspect of the invention different RF supplies connected to individual quadrupole assemblies may be synchronized with respect to



frequency and phase to maximize the ion transfer efficiency through the multiple quadrupole assembly.

Electrostatic lenses or electrodes may be positioned between individual multipole ion guides when multiple ion guide assemblies are configured in a mass analyzer. Alternatively, multipole ion guides may be aligned end to end with no electrostatic lens positioned between ion guide assemblies. Referring to Figure 20, electrostatic lenses 561, 566 and 567 serve the dual purpose of minimizing gas conductance between quadrupole assemblies and decoupling RF or AC voltages applied to adjacent multipole ion guides. Electrodes positioned between adjacent multipole ion guide assemblies can be configured to minimize the fringing field effects as ions pass from one ion guide assembly to the next and to minimize any capacitive coupling between different ion guide sets avoiding beat frequency distortions of the RF fields. It is one aspect of the present invention that both sides of a junction between two independent axially aligned adjacent quadrupole assemblies reside in vacuum pressure maintained sufficiently high to insure ion to neutral collisions. In one embodiment of the invention, the electrostatic lens separating two adjacent multipole ion guide assemblies is replaced by an independent RF only quadrupole with an individual RF supply. As will be described below both the higher vacuum pressure interquadrupole junction and the positioning of a quadrupole lens element between two adjacent quadrupole assemblies allows increased flexibility in conducting mass analysis functions at lower instrument costs when compared to conventional multiple quadrupole configurations. In one embodiment of the invention, individual quadrupole ion guide assemblies require separate RF, +/- DC and supplemental resonant or secular frequency voltage supplies to achieve ion mass to charge selection, CID ion fragmentation and ion trapping mass analysis functions. One aspect of the invention is the configuration of multiple quadrupole assemblies along a common axis with no electrode partitions in between. Each quadrupole assembly configured according to the invention can individually conduct mass selection, CID fragmentation and trapping of ions. One or more multiple vacuum stage quadrupole assemblies can be configured, according to the invention in a multiple quadrupole assembly. Multiple vacuum stage multipole ion guides have been described by Whitehouse and Dresch et. al. in U.S. Patents 5,652,427, 5,89,111 and U.S. Patent Application Number 08/694,542.

Separate RF voltage supplies providing RF voltage to individual multipole ion guide assemblies in the present invention can be operated with a common frequency and phase to minimize RF fringing field effects. Each quadrupole assembly can have different RF amplitude applied during mass to charge selection and/or ion CID fragmentation operation. Eliminating the electrodes between quadrupole ion guide assemblies increases ion transmission efficiency and allows ions to be directed forward and backward between quadrupole ion guide assemblies. Efficient bi-directional transport of ions along the axis of a multiple quadrupole assembly allows a wide range analytical functions to be run on a single instrument. As mentioned above, one aspect of the invention includes RF quadrupoles configured between each analytical quadrupole assembly to minimize any fringing fields or capacitive coupling due to interquadrupole differences in RF amplitude, +/- DC voltage and resonant frequency voltages. In another aspect of the invention, the RF only quadrupoles may be configured as RF only segments of each quadrupole assembly capacitively coupled to the adjacent quadrupole ion guide RF supply. In yet another aspect of the invention, the junctions between individual quadrupole assemblies are located in the higher pressure vacuum region where little or no axial pressure gradient exists at the junction between quadrupole assemblies. Ion collisions with the background gas serve to damp stable ion trajectories to

the quadrupole centerline where fringing field effects between quadrupoles are minimized. This collisional damping of ions trajectories by the background gas aids in maximizing ion transmission in the forward and backward direction between individual quadrupole ion guide assemblies even when different applied RF, DC and secular frequency AC fields are present between adjacent quadrupoles.

Triple quadrupoles, three dimensional ion traps, hybrid quadrupole-TOFs, hybrid magnetic sector and Fourier Transform (FTMS) mass analyzers have been configured to perform MS/MS analysis. Ion traps and FTMS mass analyzers can perform MS/MS<sup>n</sup> analysis, however, ion CID fragmentation is performed with relatively low energy resonant frequency excitation. CID fragmentation in triple quadrupoles and hybrid quadrupole-TOF mass analyzers is achieved by acceleration of ions along the quadrupole axis into a collision cell referred to herein as DC acceleration CID fragmentation. Ions are generally accelerated with a few to tens of eV in quadrupole DC acceleration CID fragmentation. Hybrid or tandem magnetic sector mass analyzers can perform high energy DC acceleration ion fragmentation with ions accelerated into collision cells with hundreds or even thousands of electron volts. In conventional triple quadrupoles as shown in Figure 20 and in hybrid quadrupole TOF mass analyzers, where the third quadrupole in a triple quadrupole has been replaced by a TOF mass analyzer, a single mass to charge range is selected in the first analytical quadrupole by applying appropriate RF and +/-DC potentials to the quadrupole rods. The mass to charge selection resolution in quadrupole ion guides operated in low vacuum pressures is limited in part by the rapid ion transit time through the quadrupole length. The single mass to charge range selected from a continuous ion beam with the first quadrupole (quadrupole 554 in Figure 20) is accelerated into the multipole ion guide collision cell (multipole ion guide 555 in Figure 20) with sufficient energy to cause CID fragmentation. Fragment ions exiting the collision cell are mass analyzed by a second analytical quadrupole (quadrupole 556 in Figure 20) or a TOF mass analyzer, in hybrid TOF mass spectrometers. The MS/MS analysis functions performed using conventional triple quadrupoles and hybrid TOF instruments are limited to a single mass to charge range selection step, DC acceleration CID fragmentation with continuous ion beam operation.

Three dimensional ion traps can be operated with single or multiple mass to charge range selection followed by ion fragmentation analytical steps in the same ion trapping volume. Single or multiple MS/MS analysis steps can be achieved in three dimensional quadrupole ion traps by applying the appropriate RF, DC and resonant frequency ejection and excitation secular AC potentials in a step wise sequence. The space charge of trapped ions in a three dimensional ion trap imposes performance restrictions not encountered in non trapping triple quadrupole operation. Both quadrupole ion guides operated as mass filters in triple quadrupoles and three dimensional ion traps are scanning mass analyzers which imposes limitations with respect to mass spectral acquisition rates when compared to non scanning Time-Of-Flight mass analyzers. Triple quadrupoles operate with a continuous ion beam delivered from an ion source. The three dimensional ion trap performs analysis in a batch-wise manner imposing duty cycle limitations when ions are delivered from a continuous beam ion source. Three dimensional ion traps typically operated in RF mode using added resonant frequency AC waveforms with ion trapping to conduct mass to charge selection and CID ion fragmentation. Mass to charge selection is conducted in triple quadrupoles by applying RF plus +/- DC to the quadrupole rods in non trapping mode. CID ion fragmentation in triple quadrupoles is performed with DC acceleration fragmentation. Mass to charge selection is

performed in the presence of collision gas in three dimensional ion traps whereas quadrupoles conducting mass to charge selection in triple quadrupoles operate in a vacuum region with pressure maintained sufficiently low to minimize or eliminate ion to neutral collisions. Multiple multipole ion guides are configured in the invention in a region of higher background vacuum pressure. Each multipole ion guide can be operated in trapping mode, mass to charge selection mode and CID ion fragmentation mode using RF, +/- DC and applied resonant AC waveforms. To detect an ion trapped in a three dimensional ion trap, the ion must enter an unstable trajectory and be ejected through an endcap of the ion trap. In contrast, ions released axially from the end of multipole ion guide operated in ion trapping mode are in a stable trajectory. Consequently, a portion of the ions trapped in a multipole ion guide can be released while ions continue to enter the same ion guide. Ions trapped in a multipole ion guide are free to move along the ion guide axis so the term two dimensional trapping is used when referring to trapping in multipole ion guides. As will become apparent in the description of the invention given below, two dimensional ion trapping in multipole ion guides allows increased analytical flexibility when compared with three dimensional ion trap operation. MS/MS<sup>n</sup> analysis functions can be performed using resonant frequency excitation or DC acceleration CID fragmentation or combinations of both. The invention allows the full range of analytical three dimensional ion trap and triple quadrupole functions in one instrument and allows the performing of additional mass analysis functions not available with current mass analyzers.

In another embodiment of the invention the analytical functionality of triple quadrupoles, three dimensional ion traps and hybrid quadrupole TOF mass analyzers are configured into a single instrument. The invention includes but is not limited to resonant frequency CID ion fragmentation, DC acceleration CID fragmentation even for energies over one hundred eV, RF and +/-DC mass to charge selection, single or multiple mass range RF amplitude and resonant frequency ion ejection mass to charge selection, ion trapping in quadrupole ion guides and TOF mass analysis. Using the mass analysis capabilities described, the hybrid quadrupole TOF according to the invention can operated with several combinations of MS/MS<sup>n</sup> analysis methods. For example, MS/MS<sup>n</sup> where  $n > 1$  can be performed using DC acceleration fragmentation for each CID step or combinations of resonant frequency excitation and DC acceleration CID ion fragmentation. Ion trapping with mass to charge selection or CID ion fragmentation can be performed in each individual quadrupole assembly without stopping a continuous ion beam. These techniques, according to the invention, as described below increase the duty cycle and sensitivity of a hybrid quadrupole-TOF during MS/MS experiments. Alternatively, MS/MS<sup>n</sup> analysis can be performed with or without trapping of a continuous ion beam during mass selection and ion fragmentation steps. The hybrid quadrupole-TOF configured according to the inventions is a lower cost bench-top instrument that includes the performance capabilities described in U.S. Patent Numbers 5,652,427 and 5,689,111 and U.S. Patent Application Numbers 08/694,542 and 60/021,184, which are fully incorporated herein by reference, included herein by reference. Emulation and improved performance of prior art API triple quadrupole, three dimensional ion trap, TOF and hybrid quadrupole TOF mass analyzer functions can be achieved with the hybrid quadrupole TOF mass analyzer configured according to the invention. The assemblies of multiple quadrupole ion guides configured according to the invention can be interfaced to all mass analyzer types, tandem and hybrid instruments and most ion source types that produce ions from gas, liquid or solid phases.

## Summary of the Invention

Atmospheric Pressure Ion Sources including Electrospray (ES) and Atmospheric Pressure Chemical Ionization (APCI) sources have been interfaced to single and triple quadrupole ion guide, three dimensional ion trap, Magnetic Sector, Fourier Transform, Time-Of-Flight and recently hybrid quadrupole-TOF mass analyzers. It is one aspect of the invention that embodiments of the invention can be interfaced to atmospheric pressure ion sources. In another aspect of the invention, embodiments of the invention can be configured in single or triple quadrupole mass analyzers or configured in hybrid three dimensional ion trap, Magnetic Sector, Fourier Transform and Time-Of-Flight mass analyzers interfaced to atmospheric pressure ion sources or ion sources that produce ions in vacuum.

The invention, as described below, includes a number of embodiments. Each embodiment contains at least one multipole ion guide located in and operated in a higher background pressure vacuum region where multiple collisions between ions and neutral background gas occur. Although the invention can be applied to multipole ion guides with any number of poles, the description will primarily refer to quadrupole ion guides. In one embodiment of the invention, the quadrupole ion guide is configured in a vacuum region with background pressure maintained sufficiently high to cause collisional damping of the ions traversing the ion guide length. Each analytical quadrupole ion guide, positioned in the higher pressure vacuum region, can be operated in trapping mode, single pass ion transmission mode, single or multiple mass to charge selection mode and/or resonant frequency CID ion fragmentation mode with or without stopping a continuous primary ion beam. In one embodiment of the invention, a high pressure quadrupole ion guide is operated to achieve single or multiple mass to charge range selection by ejected unwanted ions traversing or trapped in the quadrupole volume defined by the inner rod radius ( $r_0$ ) and rod length. Unwanted ion ejection is achieved by applying resonant or secular frequency waveforms to the ion quadrupole rods over selected time periods with or without ramping or stepping of the RF amplitude. In yet another embodiment of the invention ion, +/-DC potentials are applied to the poles of the quadrupole ion guide during mass to charge selection. The +/- DC potentials are applied to the quadrupole rods or poles while ramping or stepping the RF amplitude and applying resonant frequency excitation waveforms to eject unwanted ion mass to charge values. In another embodiment of the invention, at least one quadrupole ion guide positioned in a higher pressure region and operated in mass to charge selection and/or ion CID fragmentation mode is configured as a segmented or sectioned multipole ion guide. The segmented ion guide may include two or more sections where the RF voltage is applied to all segments from a common RF voltage supply. In one embodiment of the invention at least one segment of the segmented quadrupole is operated in RF only mode while at least one other segment is operated in mass to charge selection and/or CID ion fragmentation mode. Individual DC offset potentials can be applied to each segment independently allowing trapping of ions in the segmented quadrupole assembly or moving of ions from one segment to the an adjacent segment.

In another embodiment of the invention a segmented multipole ion guide is configured such that at least one segment extends continuously into multiple vacuum stages. A portion of the multiple vacuum stage multipole ion guide is positioned in a vacuum region where the pressure in the ion guide volume is maintained sufficiently high to cause multiple ion to neutral collisions as the ions traverse the segmented ion guide length. The RF voltage is

applied from a common RF voltage supply to all segments or sections of the multiple vacuum stage multipole ion guide. At least one section of the segmented multiple vacuum stage multipole ion guide can be operated in ion trapping mode, single pass ion transmission mode, single or multiple mass to charge selection mode and/or resonant frequency CID ion fragmentation mode with or without stopping a continuous primary ion beam. In one embodiment of the invention, one or more segments of the multiple vacuum pumping stage ion guide are operated in RF only mode while at least one segment is operated in mass to charge selection or CID ion fragmentation mode. Mass to charge selection conducted in at least one segment of the multiple vacuum stage segmented ion guide can be achieved by applying RF and +/- DC potentials to the ion guide poles. Alternatively, ejection of unwanted ions in mass to charge selection mode can be achieved by applying resonant frequency waveforms with or without stepping or ramping the RF amplitude. The range of frequency components required to eject unwanted ion mass to charge values can be reduced by adding +/- DC voltage to the rods with or without varying the RF amplitude during ion mass to charge selection operation. In one embodiment of the invention, individual offset potentials can be applied to different segments of the multiple vacuum stage multipole ion guide. Offset potentials can be applied to individual ion guide segments to trap ions within the volume defined by the surrounding segmented ion guide poles or to move ions from one segment to the next. The background vacuum pressure along at least one segment of the multiple vacuum stage ion guide varies along the axial length of said segment.

The invention can be configured with several types of ion sources; however, the embodiments of the invention described herein comprise mass analyzers interfaced to atmospheric pressure ion sources including but not limited to Electrospray, APCI, Inductively Coupled Plasma (ICP) and Atmospheric Pressure MALDI. In the embodiments described, the primary source of background gas in the multipole ion guides configured in higher pressure vacuum regions is from the Atmospheric Pressure Ion source itself. This configuration avoids the need to add additional collision gas to a separate collision cell positioned in a lower pressure vacuum region. Elimination of a separate collision cell in an API mass analyzer, reduces the vacuum pumping speed requirements, system size and complexity. Reduced size and complexity lowers the mass analyzer cost without decreasing performance or analytical capability. As will become clear from the description given below, a mass analyzer configured and operated according to the invention has increased performance and analytical range when compared with triple quadrupoles, three dimensional ion traps and hybrid quadrupole TOF mass analyzers as described in the prior art.

In another embodiment of the invention, individual multipole ion guide assemblies are configured along a common centerline where the junction between two ion guides is positioned in a higher pressure vacuum region. Ion collisions with the background gas on both sides the junction between two axially adjacent multipole ion guides serve to damp stable ion radial trajectories toward the centerline where fringing fields are minimized. Forward and reverse direction ion transmission efficiency between multipole ion guides is maximized by minimizing the fringing fields effects at the junction between two multipole ion guides. An electrostatic lens may or may not be positioned between two adjacent quadrupole assemblies.

In another aspect of the invention, no electrode is configured in the junction between two adjacent quadrupole ion guides configured along the common quadrupole axis. The two adjacent quadrupole assemblies, configured according to the invention have the same radial cross section pole dimensions and pole elements are axially aligned at the junction between

the two quadrupole ion guides. Each quadrupole assembly has an independent set of RF, resonant frequency, +/- DC and DC offset voltage supplies. In another aspect of the invention, common RF frequency and phase and common DC polarity is maintained on adjacent and axially aligned poles of adjacent axially aligned quadrupole ion guides. The RF amplitude, resonant frequency waveforms, +/- DC amplitude and the DC offset potentials applied to the poles of adjacent quadrupole ion guides can be independently adjusted for each quadrupole ion guide assembly. Adjustment of relative DC offset potentials allows ions with stable trajectories to move in the forward or reverse direction between two adjacent quadrupoles with high transmission efficiency due to minimum fringing field effects. In another aspect of the invention, at least one segmented quadrupole ion guide assembly is configured in axial alignment with another quadrupole ion guide assembly where the junction between the two quadrupole ion guide assemblies is positioned in a region of higher background pressure. The junction between the adjacent quadrupole ion guides may or may not be configured with an additional electrode. Alternatively, the junction between two adjacent quadrupole assemblies is configured with an axially aligned quadrupole assembly operated in RF only mode. RF and DC potentials are supplied to this junction quadrupole from power supplies independent from those supplying the two adjacent quadrupole assemblies. In another aspect of the invention at least one quadrupole ion guide that extends continuously into multiple vacuum pumping stages is configured in axial alignment adjacent to another quadrupole ion guide assembly. It is another aspect of the invention that at least one section of at least one quadrupole in the above listed axially aligned quadrupole combinations is operated in mass to charge selection and/or CID ion fragmentation mode. Mass to charge selected ions traversing one quadrupole assembly can be accelerated from one quadrupole into an adjacent quadrupole through an offset voltage amplitude difference sufficient to cause CID ion fragmentation. The background gas present in the region of the junction between the two adjacent quadrupole ion guides serves as the collision gas for ions axially accelerated from one quadrupole ion guide into the next. Forward or reverse direction ion acceleration with sufficient offset voltage amplitude differential applied between quadrupole assemblies can be used to fragment ions through DC acceleration Collisional Induced Dissociation.

At least one section of each quadrupole ion guide configured in a multiple quadrupole axially aligned assembly is configured to operate in ion trapping or single pass ion transmission mode, single or multiple mass to charge selection mode and resonant frequency CID ion fragmentation modes.  $MS/MS^n$  analytical functions can be achieved by running mass to charge selection in conjunction with DC acceleration CID ion fragmentation. DC acceleration fragmentation is achieved by accelerating mass to charged ions in the forward or reverse direction between adjacent ion guides. Alternatively, ions can be fragmented using resonant frequency excitation CID fragmentation in the volume defined within an ion guide segment in at least one quadrupole ion guide configured in the axially aligned set of quadrupoles. Combinations of mass to charge selection with DC acceleration and resonant frequency excitation CID fragmentation can be run in the axially aligned multiple quadrupole ion guide assembly configured in a higher pressure vacuum region to achieve a wide range of  $MS/MS^n$  analytical functions. In one aspect of the invention, the final mass analysis step in an  $MS/MS^n$  analysis sequence can be conducted using a quadrupole mass analyzer. A dual quadrupole ion guide assembly can be configured according to the invention as part of a triple quadrupole mass analyzer. Alternatively, a three quadrupole ion guide assembly can be configured according to the invention encompassing the entire triple quadrupole mass

analyzer MS and MS/MS functionality operated with continuous ion beams delivered from an Atmospheric Pressure Ion source.

In another embodiment of the invention, a multiple quadrupole ion guide axially aligned assembly wherein at least one junction between two adjacent ion guides is located in a higher pressure vacuum region, is configured with a TOF mass analyzer. At least one quadrupole ion guide in the multiple quadrupole assembly is configured to be operated in mass to charge selection and/or CID ion fragmentation mode. In one aspect of the invention, the TOF mass analyzer is configured and operated to conduct mass analysis of product ions formed in any step of a  $MS/MS^n$  analytical sequence. Single step MS/MS analysis can be achieved by first conducting a mass to charge analysis step and second an ion fragmentation step with resonant frequency excitation or DC acceleration CID within the multiple quadrupole ion guide assembly configured according to the invention. The mass to charge analysis of the resulting MS/MS product ions is conducted in the Time-Of-Flight mass analyzer. The mass to charge selection and ion fragmentation steps in the MS/MS analysis can be conducted with or without ion trapping and without stopping the primary ion beam.  $MS/MS^n$  analysis, where  $n > 1$ , can be achieved by conducting sequential mass to charge selection and ion fragmentation steps using the multiple quadrupole ion guide assembly configured according to the invention. Different methods for conducting mass to charge selection and ion fragmentation can be combined in a given  $MS/MS^n$  sequence wherein the final mass to charge analysis step or any interim mass analysis step is conducted using the TOF mass analyzer. In one embodiment of the invention, an API source is interfaced to the multiple quadrupole TOF hybrid mass analyzer configured according to the invention.

In yet another embodiment of the invention, a segmented ion guide wherein at least one segment extends continuously into multiple vacuum pumping stages is configured with a TOF mass analyzer. At least one segment of the multiple vacuum pumping stage segmented multipole ion guide is configured to conduct ion mass to charge selection and CID fragmentation with or without trapping of ions. In one embodiment of the invention at least one multiple vacuum stage segmented quadrupole ion guide is included in a multiple quadrupole ion guide assembly configured with a TOF mass analyzer.  $MS/MS^n$  analytical functions can be achieved by conducting one or more ion mass to charge selection and CID fragmentation steps in the multiple quadrupole ion guide assembly prior to conducting mass to charge analysis of the product ion population using the Time-Of-Flight mass analyzer. In one embodiment of the invention, the size of the quadrupole assembly is reduced resulting in decreased cost and size of a benchtop API multiple quadrupole-TOF mass analyzer. In one aspect of the invention, the multiple quadrupole TOF hybrid mass analyzer can be operated whereby ion mass to charge selection and fragmentation can be conducted in a manner that can emulate the MS and MS/MS mass analysis functions of a triple quadrupole mass analyzer. Alternatively, the same multiple quadrupole TOF hybrid mass analyzer can be operated whereby ion trapping, with single or multiple steps of ion mass to charge selection and ion fragmentation can be conducted in a manner that can emulate the MS and  $MS/MS^n$  mass analysis functions of three dimensional ion traps mass analyzers. In addition, the same multiple quadrupole TOF mass analyzer configured according to the invention can be operated with MS and  $MS/MS^n$  mass analysis functions that can not be conducted triple quadrupoles, three dimensional ion traps or by other mass spectrometers described in the prior art.

In another embodiment of the invention, multiple quadrupole ion guide assemblies configured and operated according to the invention, are included in hybrid Fourier Transform, three dimensional ion trap or magnetic sector mass spectrometers. In one embodiment of the invention, segmented multipole ion guides that extend continuously into multiple vacuum pumping stages are configured with Fourier Transform, three dimensional ion trap or magnetic sector mass analyzers.

High ion transmission efficiencies can be achieved in segmented multiple vacuum pumping stage multipole ion guides or multiple quadrupole ion guide assemblies configured according to the invention. Ions can traverse between multiple ion guides configured with the junction between adjacent axially aligned quadrupole ion guides located in a higher pressure vacuum region while remaining in stable radial trajectories. Consequently minimum loss of desired mass to charge value ions occur during trapping in or traversing through the multiple quadrupole ion guide assembly configured according to the invention. In one embodiment of the invention, the individual RF voltage supplies supplying potentials to each individual quadrupole assembly of the multiple quadrupole set have variable amplitudes but the same primary RF frequency and phase output. Consequently, ions whose mass to charge ( $m/z$ ) values have stable trajectories traversing each quadrupole ion guide assembly can remain in a stable trajectory through the entire multiple quadrupole ion guide assembly length. Ions with low axial translational or kinetic energies can be efficiently transported through multiple segmented or non segmented quadrupole ion guides enabling higher resolution in mass selection or mass analysis operation. Ions can also be trapped in selected sections of each segmented or non segmented quadrupole ion guide and transferred to an adjacent quadrupole or to the TOF mass analyzer when required to improve duty cycle and achieve a wide range of mass analysis operations. An important feature of multipole ion guides or individual segments of a segmented ion guide operated in ion trapping mode is that ions can be released from one end of an ion guide or segment simultaneously while ions continue to enter the opposite end of the ion guide or individual segment. Due to this feature, a segmented ion guide receiving a continuous ion beam can selectively release only a portion of the ions located in the ion guide into an axially aligned adjacent ion guide or other mass analyzer such as TOF. In this manner ions are not lost in between mass analysis steps. Ions can also be transferred back and forth between multipole ion guide assemblies or between segments within multipole ion guide assemblies allowing the performing of an array of mass analysis operations that are not possible with prior art mass analyzer configurations.

### **Brief Description of the Figures**

Figure 1 is a diagram of an Electrospray ion source orthogonal pulsing Time-Of-Flight mass analyzer with an ion reflector configured with three independent multipole ion guides positioned in series along a common axis. The third multipole ion guide extends continuously from vacuum stage two into vacuum stage three.

Figure 2 is a diagram of the configuration of electronic voltage supply units and control modules for the three multipole ion guide assembly and surrounding electrodes diagrammed in Figure 1.

Figure 3 is a diagram of the potentials applied to the quadrupole elements diagrammed in Figure 1 during a MS/MS analysis.



Figure 4 is a diagram of an alternative embodiment of an Atmospheric Pressure Ion Source hybrid TOF mass analyzer configured with orthogonal pulsing in the TOF mass analyzer and configured with three quadrupole ion guide assemblies, two of which are configured as segmented quadrupole ion guides.

Figure 5 is a diagram of an alternative embodiment of an Atmospheric Pressure Ion Source hybrid TOF mass analyzer configured with electrostatic lenses positioned in the junctions between adjacent multipole ion guides.

Figure 6 is a diagram of an Electrospray ion source, orthogonal pulsing Time-Of-Flight mass analyzer with an ion reflector flight tube geometry, configured with a three quadrupole ion guide assembly wherein one quadrupole ion guide extends continuously into two vacuum pumping stages.

Figure 7 is a diagram of an Electrospray ion source, orthogonal pulsing Time-Of-Flight mass analyzer with a linear flight tube geometry configured with a three segment multipole ion guide wherein one segment extends continuously into 2 vacuum pumping stages.

Figure 8 is a diagram of an Electrospray ion source, orthogonal pulsing Time-Of-Flight mass analyzer configured with a three quadrupole ion guide assembly wherein said multiple quadrupole assembly extends into 3 vacuum pumping stages.

Figure 9 is a diagram of an API TOF mass analyzer with orthogonal pulsing configured with three quadrupole ion guide assemblies, the second of which extends from vacuum stage two into vacuum stage three and the third of which is positioned in the orthogonal pulsing region of the TOF mass analyzer.

Figure 10 is a diagram of an alternative embodiment of an API source TOF mass analyzer with orthogonal pulsing configured with a two multipole ion guide assembly, the first of which is configured as a three segment multipole ion guide that extends into the second and third vacuum pumping stages and a second of which configured as an ion collision cell in the third vacuum stage.

Figure 11 is a diagram of an API TOF mass analyzer with orthogonal pulsing configured with a three segment quadrupole ion guide assembly positioned in vacuum stage two and a second and third multipole ion guide assembly positioned in vacuum stage three.

Figure 12 is a diagram of a portion of the stability diagram for a quadrupole ion guide.

Figure 13 is a diagram of the cross section of a quadrupole ion guide configured with round rods.

Figure 14 is a diagram of an Electrospray ion source quadrupole mass analyzer configured with three quadrupole ion guides with the second quadrupole ion guide extending continuously from the second into the third vacuum pumping stage.

Figure 15 is a diagram of an Electrospray source quadrupole mass analyzer configured with three quadrupole ion guides. The third quadrupole ion guide is positioned in lower pressure

vacuum stage three with an electrostatic lens configured in the junction between adjacent quadrupole assemblies two and three.

Figure 16 is a diagram of an Electrospray source quadrupole mass analyzer configured with a two quadrupole ion guide assembly located in the higher pressure second vacuum pumping stage with its exit end extending into a second ion guide positioned in low pressure vacuum stage three.

Figure 17 is a diagram of an Electrospray source multiple quadrupole mass analyzer configured with a dual quadrupole assembly with the second quadrupole of said assembly segment extending continuously from the second into the third vacuum pumping stage and configured with a second and third multipole ion guide and detector located in vacuum stage three.

Figure 18 is a diagram of an Atmospheric Pressure Chemical Ionization source single quadrupole mass analyzer configured with a quadrupole ion guide that extends continuously from the second into the third vacuum pumping stage.

Figure 19 is a diagram of a glow discharge ion source three quadrupole mass analyzer configured with the third quadrupole ion guide extending continuously from the second into the third vacuum pumping stage.

Figure 20 is a diagram of an Electrospray ion source interfaced to a conventional triple quadrupole mass analyzer.

Figure 21 is a diagram of a triple quadrupole mass analyzer wherein all three quadrupole ion guide assemblies are configured in higher background pressure vacuum stage two with the detector configured in lower background pressure vacuum stage three.

Figure 22 is a diagram of an Electrospray Ionization source interfaced to a single quadrupole ion guide mass analyzer wherein said quadrupole ion guide and the ion detector are configured in a higher background pressure vacuum stage.

Figure 23 is a diagram of an Electrospray Ionization source interfaced to a triple quadrupole ion guide mass analyzer wherein said triple quadrupole ion guide mass analyzer and the ion detector are configured in a higher background pressure vacuum stage.

#### **Detailed Description of the Inventions and Preferred Embodiments**

A multipole ion guide which extends continuously from one vacuum pumping stage into at least one additional vacuum pumping stage configured in a mass analyzer apparatus has been described in U.S. patent number 5,652,427. Ion trapping within a multipole ion guide coupled with release of at least a portion of the ions trapped within the multipole ion guide followed by pulsing of the released ions into the flight tube of a Time-Of-Flight mass analyzer flight tube is described in U.S. patent number 5,689,111. The operation of a multipole ion guide configured in an API TOF mass analyzer to achieve MS and MS/MS<sup>n</sup> analytical capability has been described in U.S. Patent Application Serial Number 08/694,542. The inventions described in the following sections include new embodiments of

multipole ion guides, new configurations of multiple multipole ion guide assemblies and their incorporation into mass analyzers with new methods of operating said multipole ion guides and mass analyzers. The inventions improve the performance and analytical capability of the mass analyzers in which they are configured while in some embodiments reducing the size and cost of said instruments when compared to conventional mass analyzer configurations.

Multipole ion guides have been employed for a wide range of functions including the transport of ions in vacuum and for use as ion traps, mass to charge filters and as a means to fragment ion species. A multipole ion guide comprises a set of parallel electrodes, poles or rods evenly spaced at a common radius around a center point. Sinusoidal voltage or alternating current (AC or RF) potentials and +/- DC voltages are applied to the ion guide rods or electrodes during operation. The applied AC and DC potentials are set to allow a stable ion trajectory through the internal volume of the rod length for a selected range of mass to charge ( $m/z$ ) values. These same AC and DC voltage potentials can be set to cause an unstable ion trajectory for ion mass to charge values that fall outside the operating stability window. An ion with an unstable trajectory will be radially ejected from the ion guide volume by colliding with a rod or pole before the ion traverses the ion guide length. Multipole ion guides are typically configured with an even set of poles, 4 poles (quadrupole), 6 poles (hexapole), 8 poles (octapole) and so on. Odd number multipole ion guides have also been described but have not been commonly used in commercial instruments. Quadrupoles, hexapoles and octapoles operating with RF or AC only voltages applied have been configured as multipole ion guides in mass spectrometer instruments. Where ion mass to charge selection is required, higher mass to charge selection resolution can be achieved with quadrupoles when compared to mass to charge selection performance of hexapoles or octapoles. Quadrupole ion guides operated as mass analyzers or mass filters have been configured with round rods or with the more ideal hyperbolic rod shape. For a given internal rod to rod spacing ( $r_0$ ), the effective entrance acceptance area through which an ion can successfully enter the multipole ion guide without being rejected or driven radially out of the center volume, increases with an increasing number of poles. A multipole ion guides configured with a higher numbers of poles, operated in RF only mode, can transfer a wider range of ion mass to charge values in a stable trajectory than a multipole ion guide configured with a lower number of poles. Due to the performance differences in multipole ion guides with different numbers of poles, a suitable choice of ion guide will depend to a large measure on its application. The term triple quadrupole is conventionally used to describe a configuration of three multipole ion guides axially aligned and positioned in a common vacuum pumping stage. RF and DC potentials applied to individual multipole ion guide assembly in a triple quadrupole are supplied from separate RF and DC supplies. The collision cell in "triple quadrupoles" may be configured as a quadrupole, hexapole or octapole ion guide and is typically operated in RF only mode.

The multipole ion guides described in the invention can be configured with any number of poles. Where an assembly of individual multipole ion guides are configured, a mixture of quadrupole and hexapole or octapoles may be preferred for optimal performance. Multipole ion guide rod assemblies have been described by Thomson et. al. in U.S. Patent Number 5,847,386 that are configured with segmented, non parallel or conical rods operated in RF only mode. Such rod configurations in operated in RF only mode with single polarity DC applied to all rods of an assembly can produce an asymmetric electric field in the z or axial direction during operation. This axial electric field can aid in pushing the ions through the

length of the ion guide more rapidly than can be achieved with a parallel set of non segmented rods for a given application. The presence of an axial field is useful in moving ions through a multipole ion guide with higher background pressure present in the multipole ion guide volume. Although, adding an axial field can aid in ion movement through the multipole ion guide assembly, the rod geometry configured to provide an axial field can compromise mass to charge selection resolution and increase the complexity and cost of fabrication. Conical or assymetric rod assemblies can be used in some embodiments of the invention where RF only operation is used for a given multipole ion guide assembly. In an effort to limit the number of embodiments presented, the invention will be described for multipole ion guides configured with parallel rod or electrode ion guide assemblies. Axial fields within a given multipole ion guide assembly are applied as described in some embodiments using RF only entrance and exit pole sections or segments.

Single section or segmented multipole ion guide assemblies can be configured such that at least one segment extends from one vacuum pumping stage continuously into at least one adjacent vacuum pumping stage. In one aspect of the invention, individual multipole ion guides having the same cross sectional geometries are configured as axially aligned assemblies with at least one junction between multipole ion guide assemblies located in a higher pressure vacuum pumping region where multiple ion to neutral gas collisions occur. Operation of multiple multipole ion guides in a higher background vacuum pressure region can be used effectively to achieve analytical functions such as collisional induced dissociation (CID) of ions in the same vacuum pumping stage where ion mass to charge selection is also performed. Segmented or non segmented multipole ion guides which extend continuously from one vacuum pumping stage into another in an atmospheric pressure ion source mass spectrometer instrument can efficiently transport ions over a wide range of background pressures. Multipole ion guides can deliver ions from an atmospheric pressure ion source to a mass analyzers including but not limited to TOF, FTMS, quadrupoles, triple quadrupoles, magnetic sector or three dimensional ion traps. Alternatively, assemblies of segmented or non segmented multipole ion guides configured with at least portion of the multiple ion guide assembly positioned in a higher vacuum pressure region can be operated directly as a mass analyzer with MS and MS/MS analytical capability.

An important feature of multipole ion guides operating in ion trapping mode is that ions can be released from one end of an ion guide assembly or segment simultaneously while ions are entering the opposite end of the ion guide assembly or individual segment. Due to this feature, a multipole ion guide receiving a continuous ion beam while operating in trapping mode can selectively release all or a portion of the ions located in the ion guide into another ion guide, ion guide segment or another mass analyzer which performs mass analysis on the released ions. In this manner ions entering a multipole ion guide from a continuous ion beam are not lost in between discontinuous or batch-wise mass analysis steps. One preferred embodiment of the invention is the configuration of a hybrid API source quadrupole TOF mass analyzer comprising an API source, an assembly of three quadrupole ion guides with at least two quadrupole mass analyzers operated in mass to charge selection and ion fragmentation modes and a Time-Of-flight mass analyzer. A multiple quadrupole ion guide assembly configured according to the invention in such a hybrid API source quadrupole TOF mass analyzer allows the conducting of a wide range of MS and MS/MS<sup>n</sup> analytical functions with high sensitivity, high mass to charge resolution and high mass measurement accuracy.

In the following description of the invention, three primary configurations are shown with alternative embodiments described for each configuration. The first embodiment is the configuration of a multiple quadrupole ion guide Time-Of-Flight hybrid mass spectrometer apparatus. Although the hybrid instrument as described includes a TOF mass analyzer, an FTMS, magnetic sector, three dimensional ion trap or quadrupole mass analyzer can be substituted for the Time-Of-Flight mass analyzer. The second embodiment is the configuration of an assembly of individual quadrupole ion guides with at least one junction between ion guides located in a higher pressure vacuum region to achieve the MS and MS/MS analytical functions similar to conventional low vacuum pressure triple quadrupole mass analyzers. The third embodiment described is the configuration of a quadrupole ion guide positioned in a higher vacuum background pressure region and operated in mass to charge selection mode. The third embodiment can be operated to perform the API MS mass analysis functions similar to conventional single quadrupole mass analyzers operated in low vacuum pressure. The smaller size higher pressure quadrupole ion guides configured according to the invention can reduce instrument cost and size while improving instrument performance and analytical capability.

A preferred embodiment of the invention is diagrammed in Figure 1. A linear assembly 8 of three independent quadrupole ion guides is configured in a four vacuum pumping stage hybrid API source-multiple quadrupole TOF mass analyzer. Referring to Figures 1 and 2, multiple quadrupole ion guide assembly 8 comprises three independent quadrupole ion guide assemblies 60, 61 and 62, positioned along common axis 5. Alternatively, quadrupole ion guide assemblies 60, 61 and 62 can be configured with six, eight or more rods or poles, however, the ion mass to charge selection resolving power that can be achieved using multipole ion guides decreases as the number of poles increases. Higher ion mass to charge selection resolution can be achieved with quadrupoles (four poles) when compared with hexapoles (six poles), octapoles (eight poles) or ion guides with more than eight poles or odd numbers of poles. Consequently, quadrupoles have been commonly used as mass analyzers or mass filters. Hexapoles and octapoles which have a broader  $m/z$  stability window and a larger effective entrance acceptance area, when compared to quadrupoles, are often used as collision cells or ion transport multipole ion guides operated in RF only mode with and without ion trapping in low and higher pressure vacuum regions. The multipole ion guides diagrammed in the preferred embodiments presented will be described as quadrupoles. However, for some embodiments configured and operated according to the invention, multipole ion guides configured with more than four poles can be readily substituted for the quadrupole ion guides configured in the embodiments described.

Quadrupole ion guide assembly 60 comprises four parallel electrodes, poles or rods equally spaced around a common centerline 5. Each pole comprises two sections. Each electrode of section 1 has a tapered entrance end contoured to match the angle of skimmer 26. Power supply module 63 applies RF, AC and DC potentials to the poles of both segments of segmented quadrupole 60. Quadrupole assembly 60, 61 and 62 are configured along common axis 5 where the junctions 7 and 10 between each independent quadrupole assemblies are positioned in higher pressure vacuum stage 72. Vacuum stages 71, 72, 73 and 74 are typically maintained at pressures 0.5 to 3 torr, 0.1 to 10 millitorr,  $1$  to  $8 \times 10^{-5}$  torr and  $1$  to  $5 \times 10^{-7}$  torr respectively. Ions experience several collisions with the neutral background gas molecules as they traverse the volume defined by quadrupoles 60, 61 and 62 in vacuum stage 72. In the embodiment shown in Figure 1, no electrostatic lenses are configured in junctions

7 and 10 between independent quadrupole assemblies 60, 61 and 62. To avoid fringing field effects and to maximize ion transmission between quadrupole assemblies, quadrupole ion guide assemblies 60, 61 and 62 are configured with the same radial cross section geometries with each adjacent pole axially aligned. In addition, independent RF generators configured in power supply modules 63, 64 and 65 are configured and tuned to apply the same RF frequency and phase to axially aligned adjacent quadrupole electrode. The phase shift between adjacent quadrupole rods should be less than 0.05 cycles to avoid fringing field effects. In the embodiment shown in Figure 2, the primary RF frequency is established by a resonant frequency operating point for quadrupole 60 and the RF power supply in power supply module 63. The primary RF frequency is fed back into controller 80 and distributed as the reference oscillator frequency to power supply modules 64 and 65 that apply potentials to quadrupole assemblies 61 and 62 respectively. Adjustable RF phase shifters 89 and 90 adjust the phase of the RF output from power supply modules 64 and 65 respectively so that axially aligned ion guide poles have the same RF frequency and phase applied. To reduce the RF power required to drive quadrupole assemblies 61 and 62, variable capacitance loads 92 and 93 can be adjusted to match the desired RF frequency with a resonant inductive and capacitance load for quadrupole assemblies 61 and 62 respectively. The same polarity DC is applied to axially aligned rods by power supply modules 63, 64 and 65 to minimize fringing field effects. Power supply modules 63 and 65 supply resonant waveforms or secular frequency AC indicated as "SF" in Figure 2 to quadrupole assemblies 60 and 62 respectively. Power supply modules 63, 64 and 65 also supply a common offset DC to the rods of quadrupoles 60, 61 and 62 respectively. +/-DC, SF and offset DC potentials may be rapidly applied to quadrupole rods through switching circuits from multiple supplies or voltages may be changed through Digital to Analog (DAC) input controls. The offset DC supplied by power supply module 60 will need to change rapidly for some analytical functions. This is accomplished by switching between multiple preset +/- DC power supplies to avoid the settling time of a DAC input change to a DC power supply. When operating with +/- DC applied, the DC offset potential is achieved by applying asymmetric + and - DC amplitudes. The outputs of multiple DC power supplies are rapidly switched to lenses 83, 26, 33, 34, 41 and 42 through +/- DC power supply modules 66 and 67 respectively to achieve the analytical functions described below.

Individual quadrupole ion guide assemblies 60 and 62 can be independently operated in mass to charge selection and ion fragmentation modes to achieve MS/MS<sup>n</sup> functions with Time-Of-Flight mass analysis. Segmented ion guide 60 is configured such that the same RF voltage supply 63 applies RF voltage to segments 1 and 2 through connections 68 and 69 respectively. Junction 6 between segments 1 and 2 is configured to allow some degree of capacitive coupling between adjacent axially aligned poles. The RF potential to segment 1 can be supplied through this capacitive coupling or supplied directly from power supply module 63. Different DC offset potentials to be applied to sections 1 and 2 of segmented ion guide 60 to direct ion movement through segmented multipole ion guide 60 or to trap ions within section 1 or 2 or both. Segment or section 1 of quadrupole assembly 60 is typically operated in RF only mode to minimize fringing field effects for ions entering section 2 when section 2 of quadrupole 60 is operated in mass to charge selection or ion fragmentation mode. Junctions 7 and 10 between quadrupole assemblies 60 and 61 and 61 and 62 respectively are configured according to the invention to minimize capacitive coupling or the resonant frequency waveforms applied to independently operating quadrupole assemblies 60 and 61. Constructive or destructive interference to applied resonant waveforms are avoided

by minimizing the capacitive coupling between quadrupole assemblies 60 and 62 during ion mass to charge selection and fragmentation operation. Quadrupole assembly 61 with independent RF and DC power supply 64 prevents or minimizes capacitive coupling between quadrupole assemblies 60 and 62 while maximizing ion transfer efficiency along the multiple quadrupole assembly axis 5. Alternatively, as shown in Figure 5, quadrupole 61 can be configured as a single flat electrode comprising an aperture centered on centerline 5 with DC applied to electrically isolate quadrupole assemblies 60 and 62. A preferred embodiment as shown in Figure 1 comprises the configuration of quadrupole 61 having the same radial cross section as quadrupoles 60 and 62 with poles axially aligned.

In an ideal quadrupole ion guide the pole shapes would be hyperbolic but commonly, for ease of manufacture, round rods are used. A cross section of a quadrupole with round rods 104, 105, 106, and 107 is diagrammed in Figure 13. The same RF, SF and DC potentials are applied to opposite pole sets (104, 106 and 105, 107) for most quadrupole operating modes. Adjacent poles have the same primary RF frequency and amplitude but a phase difference of 180 degrees. When the offset or common DC potential is subtracted, adjacent poles generally have the same amplitude but opposite polarity DC potentials applied. In addition to the primary RF potential, single or multiple resonant frequency AC waveforms voltage can be applied to the quadrupole rods to achieve ion mass to charge selection and ion fragmentation functions. A common DC offset can be applied to all rods 104, 105, 106, and 107 as well. The primary RF, opposite +/- DC, common DC and resonant frequency AC potentials can be applied simultaneously or individually to the poles of a segmented quadrupole ion guide to achieve a range of analytical functions. In a segmented ion guide assembly each section of each rod or pole are electrically insulated allowing different amplitude RF, SF and +/- DC applied to each section of a segmented ion guide assembly. Junctions 6, 7 and 10 in Figure 1 are configured to provide electrical insulation while minimizing any space charge effects that can distort the electric fields within the region bounded by the rods. Junctions 6, 7 and 10 between quadrupole assemblies 60 and 61 and 61 and 62 respectively are also configured to minimize RF field distortion to maximize stable ion transmission efficiency between individual quadrupole ion guides 60, 61 and 62 in multiple quadrupole ion guide assembly 8.

In the embodiment shown in Figure 1, segmented quadrupole assembly 60, quadrupole assembly 61 and the entrance end of multiple vacuum stage quadrupole assembly 62 are positioned in second vacuum pumping stage 72 where the operating background pressure is greater than  $1 \times 10^{-4}$  torr. At background pressures greater than  $1 \times 10^{-4}$  torr, typically maintained in the 1 to 10 millitorr range, ions traversing the multiple quadrupole assembly length will encounter collisions with the neutral background gas. One or more quadrupole assemblies of multiple quadrupole ion guide assembly 8 can be operated in mass to charge selection mode. Mass to charge selection operation can be achieved by applying a combination of RF and DC potentials, applying specific resonant frequencies at sufficient amplitude to reject unwanted ion m/z values, ramping the RF frequency or amplitude with or without +/- DC ramping or combinations of these techniques. Those portions of multiple quadrupole assembly 8 located in the higher pressure region of vacuum stage 72 can also be configured to operate in ion transfer, ion trapping, and Collisional Induced Dissociation fragmentation modes as well as m/z selection mode or with any combination of these individual operating modes. Operating a portion of multipole ion guide in higher background pressure in an API MS system can improve ion transmission efficiencies as was described in U.S. patents 5,652,427 and 4,963,736. In mass to charge filter or mass to charge selection

operating mode, ion collisions with the background gas slow down the selected ion  $m/z$  trajectories in the radial and axial directions as the ions traverse the multipole ion guide length in single pass or multiple pass ion trapping mode. Ions spending increased time in the multipole ion guide are exposed to an increased number of RF cycles. In this manner higher  $m/z$  selection resolution can be achieved for shorter multipole ion guide lengths than can be attained using a quadrupole mass analyzer with the more conventional method of operating in low background pressure collision free single pass non trapping mode. Operating multipole ion guides in mass selection mode in higher pressure background gas allows the configuration of smaller more compact mass analyzer instruments with reduced vacuum pumping speed requirements. A smaller multipole ion guide configuration reduces the cost of RF power supply electronics and the higher pressure operation reduces the vacuum system costs. An instrument configured with a segmented multipole ion guide, allows the conducting of ion mass to charge selection and ion fragmentation functions in higher background pressures while delivering the resulting ion populations into a low vacuum pressure region with high ion transmission efficiency.

Electrospray probe 15, diagrammed in Figure 1, can be configured to accommodate solution flow rates to probe tip 16 ranging from below 25 nl/min to above 1 ml/min. Alternatively, the API MS embodiment diagrammed in Figure 1 can be configured with an Atmospheric Pressure Chemical Ionization (APCI) source, an Inductively Coupled Plasma (ICP) source, a Glow Discharge (GD) source, an atmospheric pressure MALDI source or other atmospheric pressure ion source types. API sources may be configured with multiple probes or combinations of different probes in one source as is described in U.S. Patent Application Serial Number 08/( ). Ion sources that operate in vacuum or partial vacuum including but not limited to chemical Ionization (CI), Electron Ionization (EI), Fast Atom Bombardment (FAB), Flow FAB, Laser Desorption (LD), Matrix Assisted Laser Desorption Ionization (MALDI), Thermospray (TS) and Particle Beam (PB) can also be configured with the hybrid mass analyzer apparatus diagrammed in Figure 1. Sample bearing solutions can be introduced into ES probe 15 using a variety of liquid delivery systems. Liquid delivery systems may include but are not limited to, liquid pumps with or without auto injectors, separation systems such as liquid chromatography or capillary electrophoresis, syringe pumps, pressure vessels, gravity feed vessels or solution reservoirs. ES source 12 is operated by applying potentials to cylindrical electrode 17, endplate electrode 18 and capillary entrance electrode 19. Counter current drying gas 21 is directed to flow through heater 20 and into the ES source chamber through endplate nosepiece 24 opening 22. Bore or channel 57 through dielectric capillary tube 23 comprises entrance orifice 13 and exit orifice 14. The potential of an ion being swept through dielectric capillary tube 23 into vacuum may change there potential energy relative to ground as described in U.S. patent number 4,542,293. Ions enter and exit the dielectric capillary tube with potential energy roughly equivalent to the entrance and exit electrode potentials respectively. The use of dielectric capillary 23 allows different potentials to be applied to the entrance and exit ends of the capillary during operation. This effectively decouples the API source from the vacuum region both physically and electrostatically allowing independent tuning optimization of both regions. To produce positive ions, negative kilovolt potentials are applied to cylindrical electrode 17, endplate electrode 18 with attached electrode nosepiece 24 and capillary entrance electrode 19. ES probe 15 remains at ground potential during operation. To produce negative ions, the polarity of electrodes 17, 18 and 19 are reversed with ES probe 15 remaining at ground potential. Alternatively, if a nozzle or conductive (metal) capillaries are used as orifices into vacuum, kilovolt potentials can be applied to ES probe 15 with lower potentials applied to cylindrical



electrode 17, endplate electrode 18 and electrode 19 during operation. With conductive orifices or capillaries, the entrance and exit potentials are equal, so the API source potentials are no longer decoupled from the vacuum region potentials. Heated capillaries can be configured as the orifice into vacuum used with or without counter current drying gas. Capillary exit heater 25 is configured with dielectric capillary 23 to independently heat the exit end of capillary 23.

With the appropriate potentials applied to elements in ES source 12, Electrosprayed charged droplets are produced from a solution or solutions delivered to ES probe tip 16. The charged droplets Electrosprayed from solution exiting ES probe tip 16 are driven against the counter current drying gas 21 by the electric fields formed by the relative potentials applied to ES probe 15 and ES chamber electrodes 17, 18, and 19. A nebulization gas 48 can be applied through a second layer tube surrounding the sample introduction first layer tube to assist the Electrospray process in the formation of charged liquid droplets. As the droplets evaporate, ions are formed and a portion of these ions are swept into vacuum through capillary bore 57. Vacuum partition 53 includes a vacuum seal with dielectric capillary 23. If a heated capillary is configured with heater 25 as an orifice into vacuum with or without counter current drying gas, charged droplet evaporation and the production of ions can occur in capillary bore 57 as charged droplets traverse the length of capillary 23 towards first vacuum pumping stage 71. The neutral background gas forms a supersonic jet as it expands into vacuum from capillary exit orifice 14 and sweeps the entrained ions along through multiple collisions during the expansion. A portion of the ions entering first stage vacuum 71 are directed through the skimmer orifice 27 and into second vacuum stage 72.

The hybrid quadrupole TOF mass analyzer diagrammed in Figure 1 is configured with four vacuum pumping stages to remove background neutral gas as the ions of interest traverse from the API source through each vacuum stage during operation. The cost and size of an API/MS instrument can be reduced if it is configured with multiple vacuum pumping stages and the pumping speed required for each stage is minimized. Typically, three to four and in some cases more than four vacuum pumping stages are employed in API/MS instruments. With the development of interstage turbomolecular vacuum pumps, three and even four stage vacuum systems require only one rotary and one or two turbomolecular pumps to achieve satisfactory background pressures in each stage. Multipole ion guides operated in the AC or RF only mode have been configured in API/MS instruments to transport ions efficiently through second and/or third vacuum pumping stages 72 and 73 respectively. In the four vacuum pumping stage embodiment diagrammed in Figure 1, a rotary vacuum pump is used to evacuate first vacuum stage 71 through pumping port 28 and the background pressure is maintained in first vacuum stage 71 is maintained typically between 0.2 and 3 torr. Skimmer 26 forms a part of vacuum partition 52 dividing first and second vacuum pumping stages 71 and 72. Background pressures in second vacuum stage 72 can typically range from  $10^{-4}$  to  $2 \times 10^{-1}$  torr depending on skimmer orifice 27 size and the pumping speed employed in second vacuum stage 72 through vacuum pumping port 29.

Ions entering second vacuum stage 72 through skimmer orifice 27 enter segmented quadrupole ion guide assembly 60 where they are trapped radially by the electric fields applied to the quadrupole rods. The locally higher pressure in the entrance region 9 of section 1 of segmented quadrupole assembly 60 damps the ion trajectories as they pass through the quadrupole RF fringing fields. The collisional damping of ion trajectories in this

locally higher pressure region 9 results in a high capture efficiency for ions entering quadrupole assembly 60. Ion  $m/z$  values that fall within the operating stability window will remain radially confined within the internal volume described by the rods of quadrupole assembly 60. The trajectories of ions that fall within the stability window defined by the potentials applied to the rods of quadrupole segment 1 will damp towards centerline 5 while traversing the length of segment 1. Ion trajectories that have been damped to the centerline in segment 1 are efficiently transferred into segment 2 of quadrupole 60 when the appropriate relative bias voltages are applied between segments 1 and 2. For many applications segment 1 of quadrupole assembly 60 will be operated in RF only mode. Similarly, when the appropriate relative bias or offset potentials are applied between the rods of segment 2 of quadrupole 60 and the rods 3 and 4 of quadrupoles 61 and 62 respectively, ions traversing segment 2 of quadrupole 60 can pass through quadrupole 61 and into quadrupole assembly 62. Ions pass into third vacuum pumping stage 73 while traversing the length of quadrupole assembly 62. Each rod 4 of quadrupole assembly 62 passes through but is electrically insulated from vacuum partition 32. Third vacuum stage 73 is evacuated through vacuum pumping port 30. Ions exit multiple quadrupole assembly 8 at exit end 11 and pass through electrostatic lenses 33, 34, and 35 into orthogonal pulsing region 37 of Time-Of-Flight mass analyzer 40. Lens 33 is configured as part of vacuum partition 36 between third and fourth vacuum pumping stages 73 and 74.

Time-Of-Flight mass analyzer 40 is configured in fourth vacuum stage 74 and this vacuum stage is evacuated through pumping port 31. Fourth vacuum stage 74 is typically maintained in the low  $10^{-6}$  to low  $10^{-7}$  torr vacuum pressure region. TOF pulsing region 37 is bounded by electrostatic lenses 41 and 42. Ions which exit from multiple quadrupole assembly 8 move into TOF pulsing region 37. Ions traversing pulsing region 37 are either pulsed into TOF flight drift region 58 or continue through pulsing region 37 passing through orifice 55 in lens 54. By applying appropriate voltages to lens 54, electron multiplier detector 38, conversion dynode 39 and Faraday cup 56, ions passing through orifice 55 can be directed to impact on conversion dynode 39 or be collected on Faraday cup 56. Secondary electrons or photons released from conversion dynode 39 after an ion impact are detected by electron multiplier 38. In the hybrid mass analyzer embodiment diagrammed in Figure 1, ions entering TOF pulsing region 37 can be either TOF mass analyzed, detected by electron multiplier detector 38 or detected with Faraday cup 56. Ions enter TOF pulsing region 37 when lenses 41, 42 and 43 are set at the approximately the same potential. In the TOF configuration diagrammed in Figure 1, TOF flight drift region 58 is maintained at kilovolt potentials when the appropriate voltage is applied to lens 60. Negative voltage is applied to lens 60 for positive polarity ions and positive voltage is applied for negative polarity ions during TOF operation. With TOF drift region 58 maintained at kilovolt potentials, a voltage value at or near ground can be applied to pulsing lenses 41, 42 and 43 when ions are entering pulsing region 37. Positive ions are accelerated or pulsed into TOF drift region 58 by raising the potential of pulsing lens to 41 some positive voltage, raising 42 to approximately half that positive voltage and applying ground potential to lens 43. The positive ions are accelerated out of pulsing region 37 and into entrance region 49 of TOF drift region 58. The velocity of ions traversing drift region 58 remains constant until ions enter ion reflector 50 at entrance point 51. Ions entering ion reflector 50 are initially decelerated and then re-accelerated beginning at point 45, exiting the reflector at point 44. Ions traversing TOF drift region in the reverse direction are post accelerated from point 46 onto the surface of multichannel plate detector 47 where they are detected. Negative ions are pulsed from pulsing region 37 and

directed to the surface of detector 47 in a similar manner by reversing the voltage polarities. Limited by the flight time of the highest  $m/z$  value ion being detected, ions can typically be pulsed from pulsing region 37 at a pulsing rate of up to 20,000 times per second. Individual mass spectrum generated per TOF pulse can be added to produce summed mass spectra that can be saved to disk in a computer. TOF mass analyzers have been developed that can save over 100 summed spectra per second to disk. Signals generated by detector 47 can be recorded with data acquisition systems using Analog to Digital (A/D) converters or Time to Digital converters (TDC). Time-Of-Flight mass analyzer 40 has the capability of detecting full mass spectra of all  $m/z$  value ions traversing pulsing region 37. The TOF mass analysis step, initiated with an orthogonal pulsing of ions into drift region 58, is decoupled from any trapping, non-trapping, mass selection or ion fragmentation steps which occur in multiple quadrupole assembly 8 prior to the resulting ion population entering pulsing region 37. TOF mass analyzer 40 can acquire full mass spectra at maximum resolution and sensitivity with rapid spectra acquisition rates independent of the ion mass to charge selection or ion fragmentation steps conducted in multiple quadrupole assembly 8.

Provided that the ion population delivered to pulsing region 37 is properly focused with a minimum off axis component of energy, a range of analytical functions can be achieved upstream of pulsing region 37 without modifying optimal tuning of TOF mass analyzer 40. The hybrid mass analyzer embodiment diagrammed in Figure 1 is configured to allow a variety of MS and MS/MS<sup>n</sup> experiments to be conducted using a number of different ion mass to charge selection and ion fragmentation techniques. Several combinations of  $m/z$  selection and ion fragmentation and mass analysis can be performed sequentially or simultaneously using the embodiment diagrammed in Figure 1. At least five individual techniques can be used to perform collisionally induced dissociation ion fragmentation. These include:

1. DC ion acceleration through higher pressure gas in the capillary to skimmer region;
2. single or multiple ion resonant frequency excitation fragmentation in quadrupole ion guides 60, or 62 with or without ion trapping;
3. DC ion acceleration axially from one quadrupole to another or from one quadrupole segment to another in multiple quadrupole assembly 8 with or without ion trapping;
4. higher energy reverse DC ion acceleration into multiple quadrupole assembly 8 by switching potentials applied to exit lenses 33 and 34; or
5. overfilling of quadrupoles 60 or 62 during ion trapping until CID fragmentation occurs.

Each of these ion CID fragmentation techniques can be used individually or in combination in multiple quadrupole assembly 8.

At least four individual single or multiple ion mass to charge value selection techniques can be used with multiple quadrupole assembly 8 including:

1. resonant frequency rejection of unwanted ion mass to charge values with or without trapping in a given quadrupole assembly or segment of a segmented quadrupole assembly;
2. applying AC and +/- DC potentials to the rods of a quadrupole assembly or segment of a segmented quadrupole assembly to achieve ion mass to charge selection with or without trapping;

3. scanning RF amplitude or frequency to remove unwanted ion mass to charge values from a quadrupole assembly or a segment of a segmented quadrupole assembly with or without trapping; or
4. Controlling the release of trapped ions into TOF pulsing region 37 as described in U.S. patent 5,689,111.

Each mass to charge selection technique list above can applied individually or in combination in the hybrid quadrupole TOF diagrammed in Figure 1. Combinations of  $m/z$  selection and fragmentation techniques can be run to optimize performance for a given analytical application. Some examples of combining techniques to achieve optimal MS or MS/MS<sup>n</sup> performance are given below:

Mass to charge selection or ion fragmentation can be performed in a quadrupole ion guide with ion trapping. Mass to charge selection with ion trapping can be conducted with or without preventing the ions in the primary ion beam from entering the quadrupole where ion mass to charge selection or ion CID fragmentation is being conducted. Electrospray ion source 12 delivers a continuous ion beam into vacuum. By trapping and release of ions in multiple quadrupole assembly 8, a continuous ion beam from ES source 12 can be efficiently converted into a pulsed ion beam into TOF pulsing region 37 with very high duty cycle as is described in U.S. patent 5,689,111. Multiple quadrupole assembly 8 can be operated in non trapping or trapping mode where individual quadrupoles or segments of segmented quadrupoles are selectively operated in trapping or non trapping modes. Specific examples of segmented ion guide operating modes will be described below as a means to achieve MS, MS/MS and MS/MS<sup>n</sup> analytical functions with and without ion trapping. In the simplest case multiple quadrupole assembly 8 can be operated effectively as a segmented ion guide by applying the same AC and DC potentials to all segments of quadrupole assemblies 60, 61 and 62. Single quadrupole MS and MS/MS<sup>n</sup> TOF operating sequences are described in U.S. patent application Serial Number 08/694,542 and are included herein by reference. Analytical sequences employing multiple quadrupoles operating in ion mass to charge selection an ion fragmentation modes are described below.

An MS experiment with and without ion fragmentation can be run with a number analytical variations. If a specific range of ion mass to charge is of interest, one or more quadrupole ion guide in multiple quadrupole ion guide assembly 8 can be operated in  $m/z$  selection mode. Mass to charge selection operation using quadrupole assembly 60 or 62 can be conducted in ion trapping or in single pass non trapping mode. Narrowing the  $m/z$  charge range of ions entering TOF pulsing region 37 can improve the duty cycle and TOF system performance. Pulsed a reduced range of mass to charge value ions into TOF drift region 58 allows an increase in TOF pulse rate and duty cycle in non trapping ion guide operation. If a broad range of ion  $m/z$  values are pulsed into TOF drift region 58, the pulse rate is limited by the flight time of the heaviest ion  $m/z$ . If the next TOF pulse occurs before the all ions from the previous pulse impact on detector 47 then ions from the previous pulse will arrive during acquisition of the subsequent pulse causing signal noise in the mass spectrum acquired. Restricting the range of  $m/z$  ions entering TOF drift region 58 allows the setting of a maximum TOF pulse rate while eliminating chemical noise contributions from adjacent pulses. Preventing unwanted ion  $m/z$  values from entering TOF drift region 58 also allows more efficient detector response for those ion  $m/z$  values of interest. When an ion impacts a channel of a multichannel plate (MCP) detector, that channel requires a certain recovery time to replace its charge depletion. This charge depletion recovery time can be as long as one

millisecond, during which, any ion impacting on this channel would not be detected or would result in reduced secondary electron yield. For example, the arrival of ions from a strong solvent peak signal having a low  $m/z$  value may be of no interest in a particular analytical experiment but may deaden a significant number of detector channels in TOF each pulse prior to the arrival of higher  $m/z$  value ions in the same pulse. The impact of the solvent peak  $m/z$  ions on the detector may reduce the full signal from subsequently arriving ions. Radially ejecting undesired  $m/z$  value ions from the multipole ion guide prior to TOF pulsing to limit the ion population pulsed into flight tube drift region 56 to only those  $m/z$  values of analytical interest for a given application, helps to improve the TOF sensitivity, consistency in detector response and improves detector life.

Non trapping or trapping mass to charge selection can be conducted in quadrupole assembly 60 and 62. Consider an example where it is desirable to restrict the  $m/z$  range of ions entering TOF pulsing region 37 to the range from 300 to 500  $m/z$ . This can be achieved by a number of methods, a few of which are described in the following examples.

1. Segmented quadrupole assembly 60 is operated in non trapping RF only mode. Section or segment 2 of quadrupole assembly 60 is operated with a low mass cutoff of 300  $m/z$  by applying the appropriate RF and +/- DC to the poles of segment 2. Quadrupole assembly 61 is operated in non trapping RF only mode and quadrupole assembly 62 is operated in trapping mode with a high mass cutoff of 500  $m/z$ . The high mass to charge cutoff operation in quadrupole assembly 62 is achieved by applying with multiple resonant frequency ion ejection to quadrupole rods 4 while retaining an  $m/z$  stability window for  $m/z$  values below 500  $m/z$  by applying the appropriate RF and +/- DC amplitudes. Ions are trapped quadrupole assembly 62 and released into TOF pulsing region 37 by gating ions out of exit end 11. The potential applied to lens 33 is switched a potential to trap ions in quadrupole assembly 62 and switched to a low potential to release ions. Alternatively, a combination switching individual high and low potentials to both lenses 33 and 34 or by switching values of the quadrupole 62 offset voltage can be used to trap and release ions from quadrupole 62 respectively. Such ion trapping and-release techniques are described in U.S. Patent Number 5,689,111. Ions trapped in quadrupole assembly 62 are prevented from moving back into quadrupole assembly 60 by applying the appropriate relative offset potentials to poles 3 of quadrupole assembly 61 and the poles of segment 2 of quadrupole assembly 60. In this manner, ions moving through multiple quadrupole ion guide assembly 8 which have mass to charge values above 500 and below 300 will be rejected before entering TOF pulsing region 37.
2. Segment 1 of segmented quadrupole assembly 60 is operated in non trapping RF only mode to maximize ion transmission into segment 2. RF and +/- DC amplitude values are applied to the poles of segment 2 to pass an ions with mass to charge values in range between 300 to 500. Quadrupole ion guide assembly 62 is operated in RF only trap and release mode where the ion gate release and TOF pulse delay timing is set to pulse  $m/z$  values ranging from 300 to 500 into TOF drift region 58 pulsing at a rate of 10,000 Hz. The individual DC offset potentials applied on the rods of segments 1 and 2 of quadrupole assembly 60, rods 3 of quadrupole assembly 61 and rods 4 of quadrupole assembly 62 are set to allow the transmission of ions from multiple quadrupole assembly 8 entrance region 9 into quadrupole assembly 62. The DC offset potential differences across each segment and quadrupole junction are set sufficiently low to avoid DC acceleration CID fragmentation as ions are accelerated from one segment or quadrupole into the subsequent segment or quadrupole assembly.

3. Segment 1 of segmented quadrupole assembly 60 is operated in non trapping RF only mode to maximize ion transmission into segment 2. A range of resonant excitation frequencies is added to the RF potential applied to the rods of segment 2 to reject ions above  $m/z$  500 and below  $m/z$  300. Segment 4 is operated in RF only trap and release mode Pulsing at a rate of 10,000 Hz. DC offset potential differences across each segment or quadrupole junction are set to move ions in a forward direction through multiple quadrupole assembly 8 without causing DC acceleration CID fragmentation of ions.

Other combinations of multiple quadrupole 8 operation can be performed to achieve selected mass to charge values delivered into TOF drift region 58. Based on analytical objectives, the choice of  $m/z$  selection or fragmentation in each multipole ion guide segment should be made to maximize performance, particularly with respect to ion transmission efficiency. The application of RF and +/- DC to achieve mass selection in quadrupoles may decrease the effective entrance ion acceptance aperture potentially reducing ion transmission efficiency for the ion mass to charge values of interest. If mass to charge selection can be achieved with resonant frequency excitation ejection of unwanted ions, the quadrupole is operating essentially in RF only mode so that the effective entrance ion acceptance area or aperture is not reduced. Mass to charge selection with resonant frequency excitation ejection of unwanted ions also allows the selection of separate multiple ion  $m/z$  values where ion  $m/z$  values falling between selected ion  $m/z$  values are ejected. If a narrow ion  $m/z$  selection was desired say 1 mass to charge unit wide for an MS/MS experiment rather than the 200  $m/z$  range given above, then the  $m/z$  selection technique which yields the highest transmission efficiency would be selected. Resonant frequency excitation ejection or combined RF and DC  $m/z$  selection techniques with trapping to achieve higher resolution  $m/z$  selection can be applied uniformly or in combination to individual quadrupole assemblies 60, 61 and 62 or single or multiple segments of quadrupole assembly 60. Ion trapping during ion mass to charge selection allows the ion population in a given segment or quadrupole to be exposed to more RF cycles before being released to an adjacent segment, effectively increasing mass to charge selection resolution. Ion collisions with the background neutral gas pressure in second vacuum stage 72 aid in maintaining stable ion trajectories in multiple quadrupole assembly 8 for those ions which fall in the ion guide stability window. Trapping ions in a given segment or quadrupole assembly allows time for ions which fall outside the stability window, established by the voltages applied to the poles or each segment or quadrupole assembly to be ejected from the quadrupole volume in the presence of ion to neutral gas collisions. The exit end of quadrupole assembly 62 resides in a low pressure region where ion to neutral collisions are minimized or eliminated. Due to the lack of collisional damping effects in this low pressure portion of quadrupole assembly 62, ion  $m/z$  values not falling in the stability region as established by the potentials applied to rods 4, can be more rapidly ejected from the ion guide volume.

Although different RF frequencies can be applied to the rods of each segment or quadrupole assembly of multiple quadrupole ion guide 8, applying the same RF frequency and phase to quadrupole assemblies 60, 61 and through 62 minimizes the fringing field effects experienced by ions traversing between segment or quadrupole assemblies and maximizes the efficiency of ion transfer from one segment or quadrupole to the next. Ion  $m/z$  values falling within the stability region can move freely in either forward or backward directions from one quadrupole assembly or segment to an adjacent quadrupole or segment when the same RF frequency and phase is applied. The RF amplitude, however, may be set to different values

for each segment or quadrupole assembly to conduct different analytical functions from one quadrupole assembly to the next. At least a portion of each quadrupole assembly 60, 61 and 62 is located in a region of higher background pressure so each quadrupole assembly can individually or jointly conduct mass to charge and/or CID ion fragmentation. Reduction in cost of electronics can be achieved if the RF potential applied to each quadrupole assembly in multiple quadrupole assembly 8 is supplied from a single RF supply. A single RF supply, however, would reduce the range of analytical capability for the hybrid TOF diagrammed in Figure 1. Tradeoffs between system cost and instrument performance can be decided based on specific analytical applications requirements. In an instrument with the most analytical capability, the set of poles of each quadrupole assembly 60, 61 and 62 of multiple quadrupole assembly 8 are connected to individual and independently controlled, +/- DC, RF and secular or resonant frequency supplies as diagrammed in Figure 2. A range of analytical functions can be achieved by independently controlling the RF frequency, amplitude, offset DC amplitude, +/- DC amplitude and the resonant frequency amplitude and frequency spectrum. The amplitude and frequency components of a resonant waveform delivered from independent waveform generators in power supply units 63 64 and 65 of Figure 2 can be used to apply simple or complex AC wave forms to the poles of quadrupoles 60, 61 and 62. The applied set of secular frequency waveforms can be applied to achieve a range of simultaneous or sequential mass to charge selection and/or CID fragmentation analytical functions. Minimally, each segment of each quadrupole ion guide assembly has an independent DC offset supply or supplies where the DC offset value for a given segment of each quadrupole assembly can be rapidly switched during an analytical sequence.

Conversion dynode 39 with detector 55 has been configured to detect ions which traverse pulsing region 37 and are not pulsed into TOF drift region 58. Segment 2 of quadrupole assembly 60 or quadrupole assembly 62 multiple quadrupole ion guide 8 can be operated in non trapping mass to charge selection scan mode with ions detected by detector 38. Alternatively ions can be fragmented with resonant frequency excitation in quadrupole assembly 60 while mass to charge scanning quadrupole 62. Multiple quadrupole assembly 8 can be operated in triple quadrupole mode by selecting mass to charge value ions in quadrupole assembly 60, DC accelerated the mass to charge selected ions into quadrupole 61, operating in RF only mode, with sufficient energy to cause CID fragmentation and mass to charge scanning quadrupole 62 and detecting the fragment ion peaks with detector 38. Ions exiting segment four pass through TOF pulsing region 37 and through aperture 55 of lens 54 where they are detected on detector 38. Alternatively, ions can be detected using Faraday cup 56. Detector 38 and Faraday cup 56 can be used as diagnostic tools or in some analytical applications. The use of TOF to generate full mass spectrum from ions exiting quadrupole assembly 62 will yield higher analytical duty cycle and hence sensitivity when compared with analytical techniques utilizing mass to charge scanning of quadrupole 62 of multiple quadrupole ion guide assembly 8.

Quadrupole assemblies 60, 61 and 62 configured in multiple quadrupole assembly 8 are operated individually and jointly in both trapping and non trapping modes with DC acceleration fragmentation and resonant frequency excitation CID fragmentation and mass to charge selection with RF and +/- DC and resonant frequency ejection of unwanted ions. Optimal quadrupole geometries, segmentation, gas pressure and composition, RF and +/- DC amplitudes and secular frequencies applied and the timing of applying RF, +/- DC and SF potentials may not be the same for each analytical function mentioned above and will vary

with the mass to charge of an ion of interest. Specific variables and operating conditions that require optimization include but are not limited to the following:

1. quadrupole geometries;

A smaller rod to rod spacing ( $r_0$ ) provides a shorter distance for an ion to travel before being ejected from the quadrupole ion volume in resonant frequency excitation mass to charge selection. Smaller  $r_0$  also allows less neutral gas conductance through multiple vacuum stage ion guides. Conversely, smaller rod to rod spacing reduces the quadrupole trapping volume potentially causing space charge effects to increase more rapidly in trapping mode. Non hyperbolic quadrupole rods create non quadrupole fields or higher order (hexapole, octapole etc. field components) in the quadrupole ion guide volume when sinusoidal potentials are applied. The addition of higher multipole fields to improve performance has been practiced extensively in three dimensional ion trap construction and operation. The length of each quadrupole segment or assembly will effect the number of RF cycles to which an ion in single pass mode will be exposed.

2. neutral gas composition

In DC acceleration CID ion fragmentation, a heavier neutral gas is favored to improve ion fragmentation efficiency for a given ion acceleration energy. In resonant frequency excitation CID ion fragmentation, a lighter gas may be favored to reduce the center of mass collisional energy and the potential losses from fragment ion scattering. The invention includes the addition of a supplement gas in the second vacuum stage as diagrammed in Figure 4 to allow a partial change ion collision gas and to introduce reactive gas if desired in analytical applications that may require it.

3. neutral gas pressure

A longer mean free path between collisions or lower pressure is favorable for ejecting unwanted  $m/z$  value ions without premature fragmentation. A shorter mean free path may be favored in DC acceleration fragmentation.

4. Variable frequency and amplitude secular frequency waveforms

Optimization of the frequency and amplitude composition of secular waveforms and the timing sequence of applying said waveforms to maximize performance for ion mass to charge isolation and resonant frequency excitation CID ion fragmentation is highly dependent on the analytical application.

5. RF and +/-DC amplitudes

The amplitudes of the RF and +/- DC potentials applied to the rods of a given quadrupole may be varied to effectively shift the resonant frequency of a given mass to charge value ion during ion mass to charge ion isolation or resonant frequency CID ion fragmentation.

6. DC offset differential between quadrupole assemblies

A longer DC acceleration of ions through the background gas may result in less scattering losses when compared with a single rapid acceleration in some applications. Multiple segments allow the gradual acceleration of ions in the presence of an RF field.

Alternative embodiments of the invention as described herein provide different tradeoffs to optimize the variables listed above for different analytical applications.



Higher resolution mass to charge selection is generally required when conducting MS/MS<sup>n</sup> functions than is needed in MS analysis as described above. Resolution is a function of the ion mass to charge values that can, in a stable trajectory, pass through or are trapped in a quadrupole ion guide compared with those ion mass to charge values that are ejected from the quadrupole ion guide. Typically, quadrupoles 60, 61 and 62 of multiple quadrupole assembly 8 are operated to pass or trap ions with mass to charge values that are stable in the first stability region 102 as shown in Figure 12. Solving the equations of ion motion in a quadrupole ion guide as described by Dawson, Chapter II of "Quadrupole Mass Spectrometry and Its Applications", Elsevier Scientific Publishing Company, New York, 1976, the first stability region can be determined by the solution of the Mathieu parameters  $q_u$  and  $a_u$  where:

$$a_u = a_x = -a_y = 4zU / m\omega^2 r_0^2 \quad (1)$$

$$q_u = q_x = -q_y = 2zV / m\omega^2 r_0^2 \quad (2)$$

U is the +/- DC amplitude, m is the ion mass, z is the ion charge, V is the RF amplitude,  $r_0$  is the distance from the centerline to the quadrupole rod inside surface and  $\omega (= 2\pi f)$  is the angular frequency of the applied RF field. Solutions for the equations of motion plotted along iso- $\beta$  lines as a function of  $q_u$  and  $a_u$  are given in Figure 12. Only those ions having mass to charge values that fall within operating stability region 102 as shown in Figure 12 have stable trajectories in the x and y (radial) directions during ion trapping or ion transmission operating mode in a quadrupole ion guide. In low vacuum pressure quadrupole ion guide operation, mass to charge selection is typically conducted by operating near apex 100 of stability region 102 where  $a_u = 0.23699$  and  $q_u = 0.70600$ . As noted by Dawson, ions with mass to charge values that fall close to the stability diagram boundary increase their magnitude of radial oscillation causing loss of ions due to collisions with the rods. Operating a quadrupole ion guide close to apex 100 of stability diagram 102 increases resolution in +/- DC and RF mass to charge selection but causes loss of ions of the selected mass to charge value. The precise position of the stability boundary for a specific ion mass to charge can be modified by physical, electrical and ion space charge factors. Imperfections in the electric fields within the quadrupole ion guide volume due to non ideal rod dimensions or shape or electronic control tolerances, ion location in the quadrupole field and space charge in the quadrupole ion guide can contribute to inaccuracies in the precise position of the stability region boundaries for a given ion species. For example, round shaped rods cause higher order fields to occur within the quadrupole volume leading to distortion of the boundaries of stability region 102. In the invention disclosed herein, mass to charge selection is conducted in the presence of background gas that can cause CID fragmentation of ions with mass to charge values experiencing increased secular frequency amplitude oscillations when operating near the stability region boundary. As is known in mass to charge selection or isolation in three dimensional ion traps, unwanted ion CID fragmentation can also occur in resonant frequency ion ejection. Several operating techniques have been developed in three dimensional ion trap RF only operation to achieve higher resolution mass to charge selection with minimal loss of the selected ion species. The resonant or secular frequency,  $s_0$ , of ion motion in the radial direction while traversing or trapped in a quadrupole ion guide is approximated by the relation:

$$s_0 = q_u \omega_0 / \sqrt{8} \quad (3)$$

for  $\beta < 0.6$ . The precise secular frequency for a given ion mass to charge value can be effected by the same physical, electrical and ion space charge factors that effect the boundaries of the stability diagram.

During quadrupole ion guide mass to charge selection operation in the presence of background gas, it is desirable to maintain the radial trapping energy well sufficiently deep to efficiently trap ions while minimizing the selected ion species secular frequency oscillation amplitude. More than one operating technique can be employed to achieve these ends and the preferred method may depend on the specific mass analysis conducted. When it is desirable to simultaneously select multiple mass to charge ion species, it may be preferred to operate along the  $a_u = 0$  or RF only line applying a multiple notch resonant frequency waveform to the quadrupole rods to cause secular or resonant frequency excitation ejection of non selected ion  $m/z$  values. When selecting or isolating only one mass to charge value ion species it may be desirable to apply a small amplitude +/-DC to the quadrupole rods in addition to applying a single notch resonant frequency waveform to cause secular frequency excitation ion ejection of non selected ion  $m/z$  values. Increasing the +/- DC amplitude reduces the radial trapping energy well depth for the desired ion species but may provide a more efficient means to eliminate non selected lower and higher mass to charge value ions by reducing while reducing the range of secular frequencies required. One example of operating the hybrid TOF as diagrammed in Figure 1 in MS/MS mode with a single mass to charge value ion selection using a method according the invention is given below.

Multiple quadrupole assembly 8 configured in a hybrid TOF as diagrammed in Figure 1 is operated in MS/MS mode with a continuous ion beam delivered into segment 1 of quadrupole assembly 60. Ion mass to charge selection is conducted in segment 2 of quadrupole assembly 60 by varying the amplitude of the RF potential while applying, +/- DC and a single notch resonant frequency waveform during repetitive ion trapping and release operation. DC acceleration CID fragmentation of the selected ion species by accelerating ions from segment 2 of quadrupole assembly 60 through quadrupole assembly 61 and into quadrupole assembly 62. Quadrupole assembly 62 is operated in ion trap and release mode as described in U.S. Patent Number 5,689,111 and mass to charge analysis of the fragment ions is conducted in TOF mass analyzer 40. A diagram of some of the potentials applied to multiple quadrupole assembly 8 and TOF pulsing region 37 during MS/MS analysis is given in Figure 3. Segment 1 of quadrupole assembly 60 is operated in RF only mode. Referring to Figure 3, the different DC potentials applied to capillary exit electrode 112 and skimmer 26 and the different DC offset potentials applied to the poles of segments 1 and 2 of quadrupole assembly 60 and poles 4 of quadrupole assembly 62 remain fixed during MS/MS operation. The capillary to skimmer potentials are set to maximize the target ion transmission efficiency without causing DC acceleration CID fragmentation in the capillary to skimmer region. The potential difference between the skimmer and the DC offset potential of segment 1 of quadrupole assembly 60 is set to maximize ion transmission efficiency into segment 1. The DC offset potential applied to the poles of segments 1 and 2 of quadrupole assembly 60 are set to transfer ions efficiently from segment 1 into segment 2 without CID fragmentation. Due to the collisional damping of ion kinetic energy in segments 1 and 2, the ion energy of the parent ion beam is determined by the DC offset potential of segment 2. The frequency

and amplitude of the RF potential applied to segments 1 and 2 of quadrupole assembly 60 is set to maintain radial ion trapping operation for the selected ion mass to charge value well within stability diagram 102 and away from the stability region boundaries of  $\beta_y = 0$  and  $\beta_x = 1$ . DC potential composite curve 143 shows the DC offset potentials applied to quadrupole assemblies 61 and 62 during ion transmission mode. The different value DC offset potentials 146, 147 and 148 applied to the poles of segment 2 of quadrupole assembly 1, quadrupole 61 and quadrupole 62 respectively create DC acceleration electric fields in regions 107 and 110 sufficient to cause DC acceleration CID fragmentation of ions accelerated into quadrupole assembly 62. The selected ion DC acceleration collisional energy is set by the relative DC offset potentials applied to the poles of segment 2 of quadrupole assembly 60, quadrupole 61 and quadrupole 62. The selected ion internal energy can be elevated prior to acceleration into quadrupole assembly 62 by increasing the DC electric field between points 114 and 127 in the capillary to skimmer region, between points 127 and 109 or at point 109 between segments 1 and 2 of quadrupole assembly 60. The internal energy of the selected ion species can also increase due to some degree of resonant frequency excitation in quadrupole 60 segment 2 during ion mass to charge selection. Increasing the internal energy of a mass to charge selected ion prior to acceleration into quadrupole assembly 62, reduces the amount of DC acceleration energy required to fragment the ion.

Quadrupole assembly 62 is operated in RF only mode with the RF amplitude set to maximize ion trapping and transmission efficiency for the fragment ion mass to charge values of interest. For example if the ion species selected in quadrupole assembly 60 is multiply charged, some fragment ions would occur higher in mass to charge than the selected parent. For a singly charged ion selected in quadrupole assembly 60 all fragment ions would be lower in mass to charge than the parent. When fragmenting a multiply charged ion, the amplitude of the RF potential applied to poles 4 of quadrupole assembly 62 may be set at a higher value than when fragmenting a singly charge ion of similar mass to charge value. The RF potential applied to the rods of quadrupole 62 allows the lower  $m/z$  ions to remain in a stable trajectory unlike the higher  $m/z$  cutoff for low  $m/z$  value ions inherent in resonant frequency excitation CID fragmentation as practiced in three dimensional ion traps. The amplitude of the RF amplitude applied to poles 3 of quadrupole assembly 61 operated in RF only mode can be set to fall between the RF amplitude values set on quadrupole assemblies 60 and 62 to minimize fringing field effects in interquadrupole junctions 7 and 10. The RF potential applied aligned poles of quadrupole assemblies 60, 61 and 62 have the same frequency and phase to minimize fringing field effects at junctions 6, 7 and 10. DC waveform 143 shows the DC potentials applied to lenses 33, 34, 35, 41 and 42 are set to allow ion transmission from quadrupole assembly 62 into TOF pulsing region 37. In particular potential 151 applied to lens 41 is set near ground potential. The electric fields between points 11, 13, 134, 135 and 141 are set to optimize beam ion energy and shape in TOF pulsing region 37. DC curve 143 corresponds to point 153 drawn through timing diagram 156 shown in Figure 3.

The background pressure in the entrance end 71 of quadrupole assembly 62 serves initially as collision gas in DC acceleration CID ion fragmentation and then as the ion kinetic energy damping gas for the resulting parent and fragment ion population traversing the length of quadrupole assembly 62. DC electrical potentials applied to exit lens 33 serve to trap and release ions from exit end 11 of quadrupole assembly 62. Trapped ions that are released or gated from exit end 11 of quadrupole assembly 62 pass into TOF pulsing region 37 where they are pulsed into TOF drift region 58 and mass to charge analyzed. Ion trapping in quadrupole assembly 62 causes ions to take multiple passes back and forth through the length

of quadrupole assembly 62 before being gated out. As trapped ions move back toward entrance end 71 of quadrupole assembly 62, they pass through the higher pressure background gas present in entrance end 71 where collisional damping of ion kinetic energy occurs. Even for high energy ion acceleration into quadrupole assembly 62 sufficient to cause CID fragmentation, the resulting fragment ion kinetic energy spread can be damped to create a monoenergetic ion population in quadrupole ion guide assembly 62 having close to thermal energy spread. The average potential energy of ions traversing quadrupole assembly 62 is determined by the DC offset potential applied to poles 4 of quadrupole assembly 62. The background pressure in third vacuum stage 73 is maintained in the  $10^{-5}$  torr range or lower so that ions exiting quadrupole assembly 62 exit end 11 experience no further collisions with background gas as they move into TOF pulsing region 37. Ion molecule collisions in this region would cause scattering and defocusing of the ion beam being transferred into TOF pulsing region 37 reducing TOF performance.

To achieve ion mass to charge selection in segment 2 of quadrupole assembly 60, low amplitude +/- DC potentials, RF and a mixture of resonant or secular frequency waveforms are applied to the rods of quadrupole assembly 60, segment 2. The +/- DC, RF and secular frequency waveforms applied over time are shown in potential curves 137, 138 and 136 respectively in timing diagram 156. The amplitudes, phase and frequency components of each secular frequency in resonant waveform 136 waveform and the +/- DC potentials remain constant during ion mass to charge selection in quadrupole assembly 60 segment 2. The frequency and amplitude composition of applied secular frequency waveform 136 comprises a number of subranges as described by Wells et. al. in U.S. Patent Number 5,521,380 for mass to charge selection in three dimensional quadrupole ion traps. Creating a multiple subrange set of secular frequencies combined with modulating the RF amplitude minimizes the number secular frequency components required to eject non selected ion m/z values and minimizes selected ion losses from off resonant frequency excitation during single or multiple ion mass to charge selection. The spacing of the frequency resonant frequency components remains within a subrange. A frequency notch is maintained around the selected ion mass to charge value and the amplitudes of the frequency components on either side of the frequency notch or gap taper in amplitude as the frequencies approach the selected mass to charge notch. The RF amplitude is ramped as ions traversing segment 2 of quadrupole assembly 60, effectively changing the resonant frequency for a given ion mass to charge value. The RF amplitude ramp waveform as shown in curve 138 is asymmetric to account for the asymmetry of energy accumulation from off resonant frequencies when approaching the resonant frequency of the selected ion species from a lower or higher of resonant frequency. This asymmetry is due to the effect of higher order pole electric field components present in the segment 2 of quadrupole 60 during ion mass to charge selection or isolation operation. Ramping of the RF amplitude allows control of how much time the selected ion species spends exposed to a near resonant frequency while resident in segment 2 of quadrupole assembly 60. Higher resolution mass to charge selection with minimum loss to the desired ion species can be achieved with a careful selection of the frequency, phase and amplitude components of the resonant or secular composite waveform coupled with optimal RF amplitude ramping functions.

Higher resolution ion mass to charge selection can be achieved with the appropriate electric fields as described above applied to the rods of segment 2 of quadrupole assembly 60 if the ion population of interest spends more time resident in segment 2. Increasing the exposure of

non selected mass to charge value ions to more RF and resonant frequency cycles improves the efficiency of non selected ion ejection from segment 2 of quadrupole 60 in the presence of background gas. The same background gas effectively damps the radial oscillations of selected non excited ion species to the quadrupole 60 centerline 5. DC acceleration of ions damped to centerline 5 into quadrupole 62 minimizes scattering losses of parent and fragment ions. To increase the selected ion resident time in segment 2 of quadrupole assembly 60 ions can be trapped in and released from segment 2 in a repetitive manner by changing or switching the offset potential applied to the rods of quadrupole assembly 61. Any effect on the resonant frequencies of selected ion species due to space charging can be minimized or eliminated by choosing the appropriate fill and empty cycle time periods. Curves 139, 140 and 142 show an example of the ion trapping and release timing of ions in quadrupoles 60 and 62 synchronized with the TOF pulsing voltage applied to lens 41. Curve 139 diagrams the offset potentials applied to rods 3 of quadrupole assembly 61 during MS/MS operation. Ions are trapped in segment 2 of quadrupole assembly 60 when offset potential 148 is applied. Ions are released from segment 2 and accelerated through quadrupole 61 and into quadrupole 62 with sufficient energy to cause ion CID fragmentation when DC offset potential 147 is applied rods 3 of quadrupole 61. When increasing the DC offset trapping potential applied to quadrupole 61, an interim voltage 149 is applied briefly to clear ions from the volume of quadrupole 61 without significantly increasing the kinetic energy of said ions accelerated into quadrupole 62 above the offset potential applied to the rods of segment 2. DC offset potential 149 can be set to a value just above the offset potential of segment 2 to prevent ions from entering quadrupole 61 while allowing ions in quadrupole 61 to be accelerated into quadrupole 62. Some ions in the volume of quadrupole 61 will also return to segment 2 unfragmented when DC offset voltage 158 is applied. If desired, the offset potential applied to the rods of quadrupole 61 can be used to increase the potential energy of ions accelerated forward into quadrupole assembly 62 or backward into quadrupole assembly 60 by applying the appropriate timing and voltage amplitude to the trapping and release DC offset potentials. This pulsed ion kinetic energy increase is analogous to the backward DC acceleration CID ion fragmentation using switched potentials applied to lenses 33 and 34 as described in U.S. Patent Application Serial Number 08/694,542.

The switching of quadrupole 61 DC offset voltages is synchronized with the TOF ion pulsing and ion flight time in TOF drift region 58 so that no voltage switching occurs during ion flight time in TOF drift region 58. This avoids electrical noise spikes from occurring in the acquired mass spectrum. DC potential curve 144 occurs at timeline 154 drawn through timing diagram 156. DC voltage curve 144 shows DC trapping potentials 148 and 150 applied to the rods of quadrupole 61 and lens 33 respectively while DC potential 152 applied to TOF pulsing lens 41 is raised to accelerate ions into TOF drift tube 58. TOF mass analysis is conducted on ions pulsed into TOF drift region 58. The repetitive trapping and release of ions from quadrupole ion guide assembly 62 followed by TOF mass analysis is described in U.S. Patent Number 5,689,111. MS/MS analysis can be conducted using the application of RF, SF and DC potentials and switching sequences as described above with high efficiency ion mass to charge selection and DC acceleration CID fragmentation. The MS/MS sequence is conducted using a small compact multiple quadrupole assembly configured with a TOF mass analyzer. Alternative methods can be used to achieve efficient MS/MS analysis from the specific technique described. For example, the resonant frequency waveform, 136, can be turned off and a higher +/- DC amplitude applied to the rods of segment 2. The amplitude of the repetitive ramping of the RF is set to move the selected ion  $m/z$  value back and forth across stability diagram 102 minimizing the time the  $m/z$  value spends near stability region

boundaries of  $\beta_y = 0$  and  $\beta_x = 1$ . With this technique, ion mass to charge value ions falling above and below the selected  $m/z$  value ion species would be ejected from the quadrupole while imparting minimum excitation energy to the selected ion species. Alternatively, an excitation resonant frequency can be applied to the rods of quadrupole assembly 62 that matches the selected parent ion  $m/z$  value to aid in selectively fragmenting the parent ion. Quadrupole assemblies 60 and 62 may also be operated in ion single pass non trapping mode. Additional techniques for performing  $MS/MS^n$  analysis functions are described below.

Optimization of the RF, SF and DC potentials and electrical potential switching and ramping sequences applied to the poles of multiple quadrupole assembly 8 is effected by the background pressure maintained in second vacuum pumping stage 72 as diagrammed in Figure 1. Ion collisions with the background gas can cause desired fragmentation and undesired fragmentation, can increase the time of unstable trajectory ion ejection, can damp stable ion trajectories to the quadrupole centerline, can reduce the ion transfer time through a quadrupole length and provide a reaction media for ion to neutral gas phase reaction studies. The higher the background pressure, the larger the number of ion to neutral gas collisions occur per time period. By configuring the appropriate skimmer orifice 27 size and the appropriate vacuum pumping speed through vacuum port 29, the background pressure in second vacuum stage 72 can be varied between  $1 \times 10^{-4}$  torr to over 500 millitorr. For many of the operational sequences described below, a background pressure should be maintained in vacuum stage 72 where multiple collisions between ions and background gas occurs as ions traverse each quadrupole length. The mean free path should be maintained at a balance where efficient stable ion trajectory damping occurs, efficient DC acceleration and resonant frequency excitation CID ion fragmentation occurs yet trajectory damping does not prevent the ejection of ions in unstable trajectories within experimentally useful time frames. Typically, a background pressure between 4 and 8 millitorr is maintained in vacuum stage 72 during operation. The gas composition may be nitrogen is the only supply of background gas provided from the atmospheric pressure ion source. The background gas composition can be modified by adding additional gas such as helium or argon into vacuum stage 72 as diagrammed in the embodiment of the invention shown in Figure 4. Reactive gas may also be added to vacuum stage 72 to study ion and neutral gas reactions. In one embodiment of the invention multipole quadrupole assembly 8 was configured with an  $r_0$  of 1.25 mm and operate with an RF frequency of approximately 5 MHz.

The optimal background vacuum pressure and gas composition will be a function of the multipole ion guide geometry including pole to pole spacing, individual segment or quadrupole assembly lengths and the range of  $MS/MS^n$  functions that the instrument will be required to perform. For purposes of discussion, consider that the background pressure in second vacuum stage 72 is maintained at pressure between one to ten millitorr. One to ten millitorr is a typical operating pressure found in of three dimensional quadrupole traps and the multipole ion guide collision cells of triple quadrupoles. The background gas in three dimensional ion traps is typically helium and the background gas introduced into the collision cell of a triple quadrupole is typically argon. The gas load in second vacuum stage 72 will be primarily composed of countercurrent drying gas 21 from ES source 12. Countercurrent drying gas 21 is typically nitrogen but, depending on the analytical application may also contain carbon dioxide, sulfur hexafluoride, oxygen and residual solvent evaporated from the sample solution. The pressure and composition of the background gas in second vacuum

stage 2 can be controlled and maintained constant during MS operation allowing the optimization of applied potentials. The pressure in ES source 12 atmospheric chamber is maintained close to atmospheric pressure and the temperature in capillary bore 57 is steady state during MS operation so that the choked gas flux through capillary orifice 57 is consistent for during MS operation. In the embodiment diagrammed in Figure 1, skimmer orifice 27 is typically positioned inside the supersonic free jet zone of silence upstream of the normal shock. Consequently, the gas flux into second vacuum stage 72 is consistent over time during MS operation. The background pressure consistency in second vacuum stage 72 is primarily determined by the vacuum pumping speed through vacuum port 29. The use of turbomolecular vacuum pumps to evacuate second stage 72 provides consistent pumping speeds over extended time periods. With the ability to monitor turbomolecular pump RPM and by directly measuring the background vacuum pressure in vacuum stage 72 the background pressure can be maintained constant over extended time periods. With a consistent composition and pressure for the neutral background gas in second vacuum stage 72, repeatable results can be obtained for a wide range of experimental sequences performed.

The background pressure present in second vacuum stage 72, ions is sufficiently high to be used for ion fragmentation through CID processes but not so high that  $m/z$  selection performance or ion transmission efficiency is compromised. The configuration of segmented multipole ion guide 8 combined with TOF mass analysis diagrammed in Figure 1 allows for performing all MS and MS/MS functions of triple quadrupoles, all MS and MS/MS<sup>n</sup> functional sequences of three dimensional ion traps and can perform several MS and MS/MS<sup>n</sup> functions that are not possible with either triple quadrupoles or three dimensional quadrupole ion traps. Examples of some MS/MS<sup>n</sup> functions that can be performed with the hybrid TOF embodiment diagrammed in Figure 1 will be described below.

Four non trapping single pass primary MS/MS operating modes are used in triple quadrupoles that employ DC ion acceleration into an RF only collision cell to achieve CID fragmentation. These four operating modes include:

1. transmitting a single selected  $m/z$  range in quadrupole 1, fragmented the selected ions in the RF only collision cell while scanning quadrupole 3;
2. neutral loss scan, where quadrupole 1 and 3 are scanned simultaneously with a fixed  $m/z$  offset with fragmentation of parent ions in the RF only collision cell;
3. scanning quadrupole 1 while setting quadrupole 3 to pass a selected  $m/z$  range with fragmentation of parent ions in the RF only collision cell; and,
4. setting both quadrupoles 1 and 3 to pass different  $m/z$  values without scanning with fragmentation of parent ions in the RF only collision cell to monitor selected fragmentation events.

In the embodiment of the hybrid TOF shown in Figure 1, full fragment ion spectra are recorded in the TOF analyzer without scanning resulting in higher sensitivity and resolution performance than can be achieved in triple quadrupole operation. The hybrid TOF MS as diagrammed in Figure 1 can be operated to emulate triple quadrupole performance with full TOF mass spectra acquired replacing the third quadrupole single mass selection and mass scan analytical functions. MS/MS analysis requires the steps of mass to charge selection, fragmentation of the selected mass to charge parent ions and mass analysis of the first generation fragment or product ions. The final mass to charge selection step in any given MS/MS sequence is performed with TOF mass analyzer 40. The mass to charge selection and ion fragmentation steps are performed in multiple quadrupole assembly ion guide 8 with

additional ion fragmentation, when required, performed in the capillary to skimmer region. An MS/MS experimental sequence such as was described in the previous section can be conducted which results in fragment ions similar to those produced in a triple quadrupole MS/MS operating mode 1 listed above. Alternatively, using a different experimental sequence, fragment ion populations can result which are similar to those produced in an ion trap MS/MS experiment.

The hybrid multiple quadrupole TOF as configured in Figure 1 can be operated to simulate triple quadrupole neutral loss MS/MS operating mode 2 as listed above in which quadrupoles 1 and 3 of a triple quadrupole are scanned during data acquisition. TOF operation replacing scanning quadrupole 3 produces, full TOF spectra of fragment ions. A Reconstructed Ion Chromatographs (RIC) can be generated from acquired TOF full spectra to match triple quadrupole like neutral loss MS/MS data. To achieve this subset of neutral loss data, the hybrid multiple quadrupole TOF embodiment shown in Figure 1 can be operated in as follows:

1. segment 1 of quadrupole assembly 60 is operated in non trapping RF only mode with DC offset potentials applied that allow ions to pass into segment 2 at low energies with no CID fragmentation.
2. segment 2 of quadrupole assembly 60 is operated in non trapping ion  $m/z$  selection mode with the application of modulated RF, +/- DC and an appropriate composite resonant frequency waveform as described in the previous section. To simulate the scanning of the first quadrupole of a triple quadrupole mass analyzer, the  $m/z$  selection window of segment 2 is periodically stepped to a new value until the desired  $m/z$  range is covered. The  $m/z$  window stepping in segment 1 is synchronized with the TOF spectra acquisition so that the parent ion mass to charge of any given first generation fragment ion spectrum is known.
3. segment 3 is operated in trapping RF only mode. The different DC offset potentials applied to the poles of segment 2 of quadrupole 60, quadrupole 61 and 62 are set to accelerate ions from segment 2 into quadrupole 62 with sufficient energy to cause the desired amount of CID ion fragmentation of the selected parent ions. Ions released or gated from the exit end of quadrupole 62 and transferred into TOF pulsing region 37 are pulsed into TOF drift region 58 and mass analyzed.

Consider a neutral loss scan over the parent mass to charge range from 400 to 800. If the parent  $m/z$  window is 4  $m/z$  wide selected by segment 2 of quadrupole assembly 60, 100 steps would be required to cover the  $m/z$  range from 400 to 800. If the TOF mass analyzer is pulsed at a rate of 10,000 times per second with 1,000 pulses added for each mass spectra saved to memory, then 10 mass spectra per second would be recorded. Under these TOF data acquisition conditions, a full simulated neutral loss scan would take 10 seconds to acquire. If TOF spectra were acquired at a rate of 40 spectra per second, total acquisition time for each full simulated neutral loss scan would be 2.5 seconds, approaching typical scan speeds used in triple quadrupole neutral loss scans. The TOF full spectrum data acquired in the above listed operating sequence contains complete fragment ion information unlike the more limited information recorded from a triple quadrupole neutral loss scan or the case where the first quadrupole is scanned with the third quadrupole  $m/z$  range selection fixed. Consequently, either triple quadrupole experiment can be simulated with the above listed segmented ion guide TOF operating sequence. Variations in the above sequence can be used to achieve the same ends. For example,  $m/z$  range selection can be conducted in segment 1 or segment 1 and 2 of quadrupole assembly 60 in trapping or non trapping mode. Quadrupole ion guide



assembly 62 can be operated in trapping or non trapping mode. In trapping mode, the trapping voltage applied to lens 33 can be held low when the  $m/z$  range in segments 1 or 2 of quadrupole 60 is switched. Trapped ion fragments formed from the previous parent  $m/z$  value are then allowed to exit the trap formed by quadrupole 62. A small delay time may be added after a  $m/z$  range selection step to allow the segment 4 trap to fill prior to resuming TOF pulsing. Alternatively, parent ions may be trapped in segment 2 of ion guide 60 while fragment ions from the previous parent mass to charge value are being gated into TOF pulsing region 37 from quadrupole 62.  $M/z$  selected parent ions trapped in segment 2 are then accelerated into quadrupole 62 after the fragment ions from the previous parent ion set have been gated into TOF pulsing region 37. A new mass to charge value set of parent ions are then isolated in quadrupole 60 segment 2. The transfer of all ions trapped within segment 2 at a time when the DC offset potential applied to the rods of quadrupole 61 differs from the partial ion population release as described in the previous section. However, a continuous ion beam can be accepted into segment 1 of quadrupole assembly 60 in either operating mode, maximizing overall duty cycle.

In the above simulated triple quadrupole neutral loss scan operating mode, DC ion acceleration is employed to achieve CID first generation ion fragmentation. Alternatively, resonant frequency excitation CID fragmentation can be employed in quadrupole assemblies 61 and 62 or combinations of DC ion acceleration and resonant frequency excitation. The preferred fragmentation technique will depend on the analytical information desired. Resonant frequency excitation can be used to fragment selected ions without adding internal energy to non selected  $m/z$  values, particularly fragment product ions. Due to the multiple collisions experienced by all ion species produced in DC ion acceleration CID, the internal energy of all accelerated ions is increased including that of the produced fragment ions. Resonant frequency excitation has the disadvantage that to achieve increased fragmentation energy the amplitude of the resonant frequency is increased. To radially trap the ions being excited, the RF amplitude must be increased proportionally resulting in an increased the low  $m/z$  cutoff. Typically, when operating ion traps in MS/MS mode, the bottom one third or more of the  $m/z$  scale may be ejected to achieve sufficient resonant frequency excitation fragmentation of the parent ion or ions of interest. Both DC ion acceleration and resonant frequency excitation can be combined simultaneously or sequentially to achieve optimal MS/MS or MS/MS<sup>n</sup> performance without ejecting the lower portion of the mass to charge scale. The hybrid segmented ion guide TOF embodiment diagrammed in Figure 1 can be configured to achieve all triple quadrupole as listed above and ion trap MS/MS<sup>n</sup> functions with combinations of DC acceleration and resonant frequency excitation CID ion fragmentation operation not conducted in either triple quadrupoles or an ion traps.

A wide range of MS/MS<sup>n</sup> analysis functions can be conducted using the hybrid TOF embodiment shown in Figure 1. To simplify the description of the operational sequences required to conduct specific MS/MS<sup>n</sup> functions, the techniques used can be divided into two groups. The first group includes those that require cutting of the continuous ion source generated primary ion beam and those that require no break in the primary ion beam during operation. First some MS/MS<sup>n</sup> techniques which accept a continuous ion beam from electrospray ion source 12 will be describe below.

Consider running an  $MS/MS^2$  experiment with the embodiment shown in Figure 1. The simplest functional sequence is an extension of the  $MS/MS$  case described above where DC accelerated ion fragmentation occurs between segments 1 and 2 of quadrupole assembly 60 after non trapping mass to ion mass to charge selection is conducted in segment 1. Specifically the hybrid multiple quadrupole TOF is operated with the following sequence to achieve  $MS/MS^2$  mass analysis.

1. Segment 1 of quadrupole assembly 60 is operated in mass to charge selection mode. Selected mass to charge ions are accelerated into segment 2 with sufficient DC offset potential applied between segments 1 and 2 to cause CID fragmentation of the  $m/z$  selected ions.
2. Segment 2 of quadrupole 60 is operated trapping or non trapping mass to charge selection mode where one or more first generation product ions is selected. The  $m/z$  selected first generation product ions are then accelerated through quadrupole 61 and into quadrupole 62 applying the appropriate relative DC offset potentials to the poles of segment 2 and quadrupoles 61 and 62 to cause CID fragmentation of the selected first generation fragment ions.
3. Quadrupole 62 is operated in RF only trapping mode from which second generation fragment ions are gated into TOF pulsing region 37. The second generation fragments ions are subsequently pulsed into TOF drift region 58 and mass to charge analyzed.

Ion mass to charge selection operation in segments 1 and 2 of quadrupole assembly 60 may employ fixed or modulated RF and  $\pm$  DC mass filtering or composite resonant frequency waveform ejection of unwanted  $m/z$  ions or a combination of both as has been described above. Different  $\pm$  DC and composite resonant frequency waveform AC potentials and common RF potentials are simultaneously applied to the poles of segments 1 and 2. Ion fragmentation may be achieved using resonant frequency excitation instead of or in conjunction with DC ion acceleration fragmentation in segments 2 of quadrupole 60 and quadrupoles 61 and 62. Resonant frequency excitation can occur simultaneously with ion  $m/z$  selection in segment 2 of quadrupole assembly 60 by including the appropriate frequency notches and variation in amplitudes in the composite resonant frequency waveform applied to the poles of segment 2. Segment 2 can be operated in trapping mode by applying the appropriate relative DC offset potentials to the poles of quadrupole assembly 61 to trap ions in segment 2 of quadrupole assembly 60 or release ions from segment 2 into quadrupole assembly 62. In all  $MS/MS^n$  experiments, the relative capillary to skimmer potential can be raised to increase the internal energies of ions in the primary ion beam to facilitate ion fragmentation in multiple quadrupole ion guide assembly 8.

$MS/MS^2$  can alternatively be achieved by mixing DC ion acceleration and resonant frequency excitation ion fragmentation techniques by operating multiple quadrupole ion guide assembly 8 in the following mode.

1. Segment 1 of quadrupole assembly 60 is operated in RF only ion pass mode. Ions are transferred from segment 1 into segment 2 with low energy and with no ion fragmentation.
2. Segment 2 of quadrupole assembly 60 is operated trapping mode with ion mass to charge selection. Ions, when released from segment 2, are accelerated from segment 2 through quadrupole 61 and into quadrupole 62 with sufficient energy to cause CID fragmentation of the  $m/z$  selected ions.

3. Quadrupole assembly 62 is operated in ion trapping mode with two step  $m/z$  selection and resonant frequency excitation fragmentation of the selected first generation ion. Second generation fragment or product ions are gated into TOF pulsing region 37 and subsequently TOF mass analyzed. The  $m/z$  selection and ion CID fragmentation steps are conducted in series prior to initiating TOF mass analysis. Parent ions are trapped and accumulated in segment 2 during the first generation fragment ion  $m/z$  isolation and fragmentation steps conducted in quadrupole assembly 62. After the second generation fragment ion population has been released from quadrupole 62 and TOF mass to charge analyzed, a new set of selected mass to charge value ions are accelerated into quadrupole 62. The new first generation fragment ion population is trapped in quadrupole 62 and undergoes sequential mass to charge isolation, ion fragmentation and TOF mass analysis steps.

Quasi  $MS/MS^n$  experiments can be achieved with a continuous primary ion beam using techniques described in U.S. patent application number 08/694,542. In the techniques described, true  $m/z$  selection does not take place prior to ion fragmentation. Instead two spectra are acquired sequentially, the first with a combination of parent or fragment ions and the second with the next generation fragment ions. The first TOF mass spectrum acquired is subtracted from the second to give a spectrum containing peaks of just the  $MS/MS^n$  fragment ions. This method requires multiple component resonant frequency excitation waveforms for conducting CID excitation ion fragmentation. Using this technique, an  $MS/MS^4$  experiment can be conducted with the hybrid quadrupole TOF diagrammed in Figure 1 as described below.

Mass spectrum 1 is acquired with the following operating sequences conducted with multiple quadrupole ion guide assembly 8.

1. Segment 1 of quadrupole assembly 60 is operated in mass to charge selection mode. The resulting ion population is accelerated into segment 2 with sufficient energy to cause CID fragmentation.
2. Two component resonant frequency excitation is applied to the poles of segment 2, to induce CID fragmentation of the selected second and third generation ions. The product ions are passed through quadrupole assembly 61 into quadrupole assembly 62 without further fragmentation.
3. Quadrupole assembly 62 is operated in trapping or non-trapping RF only mode with ions transferred into TOF pulsing region 37. Ions are subsequently pulsed into drift region 58 of TOF mass analyzer 40 and mass to charge analyzed.

A second TOF mass spectrum is generated with three component resonant frequency excitation applied to segment 2 or a single resonant excitation frequency applied to poles 4 of quadrupole assembly 62 to fragment the selected third generation product ion having the matching resonant excitation frequency. The first mass spectrum acquired is subtracted from the second mass spectrum resulting in a mass spectrum containing fourth generation fragment or product ions and their specific parent ion.

An alternative  $MS/MS^n$  analysis technique can be used which may use either a continuous or non continuous primary ion beam depending on the specific analytical application. With this technique, ions are moved from one segment or quadrupole assembly to an adjacent segment

or quadrupole assembly in blocks. All ions trapped in one segment or quadrupole are transferred to the next sequential segment or quadrupole ion guide assembly before accepting a new population of ions from the previous segment or quadrupole assembly. Each segment or quadrupole assembly can independently perform single or multiple  $m/z$  selection and/or resonant frequency excitation CID ion fragmentation functions or ions are fragmented using DC acceleration CID as ions are transferred between segments or quadrupole assemblies.

The steps of an  $MS/MS^3$  analysis using this technique are listed below.

1. Segment 1 of quadrupole assembly 60 is operated in RF only mode with ion  $m/z$  selection or isolation using multiple frequency composite waveform resonant frequency ejection of unwanted ions. The relative DC offset potentials applied to the poles of segments 1 and 2 of quadrupole assembly 60 are set to accelerate ions from segment 1 into segment 2 with sufficient kinetic energy to cause DC acceleration CID ion fragmentation. The primary beam remains on at all times and ions continuously enter segment 1.
2. The relative DC offset potentials applied to the rods of segment 2 of quadrupole assembly 60 and quadrupole assembly 61 are set to trap ions in segment 2 for a given time period. Segment 2 is operated in  $m/z$  selection mode and the selected  $m/z$  value first generation fragment ions are trapped in segment 2 for the given time period.
3. The DC offset potential applied to rods 3 of quadrupole assembly 61 is then switched low to pass ions from segment 2 of quadrupole assembly 60 through quadrupole 61 and into quadrupole 62 for a time period of a duration sufficient to substantially empty segment 2 of trapped ions to the level of the continuous primary ion beam operating in single pass mode. Ions are accelerated from segment 2 of quadrupole assembly 60 through quadrupole 61 and into quadrupole 62 with sufficient kinetic energy to cause DC acceleration CID ion fragmentation. After the ion transfer period, the DC offset potential applied to poles 3 of quadrupole 61 is switched high trapping ions in segment 2 and preventing trapped ions quadrupole assembly 62 from re-entering segment 2 of quadrupole assembly 60 in the reverse direction.
4. Quadrupole assembly 62 is initially operated in  $m/z$  selection mode while ions are being transferred into quadrupole 62 from segment 2 through quadrupole 61. The potential applied to lens 33 is initially set to trap and hold ions in quadrupole assembly 62. After the DC offset potential applied to poles 3 of quadrupole assembly 61 is raised to stop ion flow from segment 2 of quadrupole assembly 60, the potentials applied to poles 4 of quadrupole 62 are switched such that quadrupole 62 is operated in RF only mode with resonant frequency excitation CID fragmentation of the selected  $m/z$  value second generation fragment ions trapped in quadrupole 62. If an  $MS/MS^3$  experiment is desired, the resulting third generation product or fragment ions trapped in quadrupole 62 are released, by switching the voltage applied to lens 33, in gated ion packets into TOF pulsing region 37 and subsequently TOF mass analyzed. If higher order  $MS/MS^n$  steps are required, additional sequential  $m/z$  selection and CID fragmentation steps can be continued with the ions trapped in quadrupole assembly 62, prior to releasing ions into TOF pulsing region 37. TOF spectra of a portion of the products ions can be acquired at each  $MS/MS$  step or at the end of the  $MS/MS^n$  sequence. While  $MS/MS$  steps are being conducted with ions trapped in quadrupole assembly 62, selected first

generation product ions continue to accumulate in segment 2 of quadrupole assembly 60.

5. When all  $n$  generation product ions trapped in quadrupole assembly 62 have been gated into TOF pulsing region 37 and subsequently TOF mass analyzed, the DC offset potential applied to poles 3 of quadrupole assembly 61 is lowered and steps 3 and 4 above are repeated.

MS/MS<sup>n</sup> analytical functions can be run using the hybrid TOF diagrammed in Figure 1 operating with a non continuous primary ion beam. Several functional sequences are possible with multiple quadrupole assembly 8 and TOF mass analyzer 40 to conduct MS/MS<sup>n</sup> analysis with a non continuous primary ion beam. U.S. patent application 08/694,542 describes the configuration of multipole ion guide TOF mass analyzer where the multipole ion guide is operated in trapping mode with sequential  $m/z$  ion selection and resonant frequency excitation CID ion fragmentation steps prior to TOF mass analysis. The addition of multiple segments and additional quadrupole assemblies configured in a higher background pressure region allows operational and analytical variations not possible when conducting MS/MS<sup>n</sup> mass analysis sequences with a single segment two dimensional trap TOF with a non-continuous primary ion beam. Unlike three dimensional ion traps or FTMS mass analyzers, the hybrid multiple quadrupole assembly TOF configuration can be configured and operated to achieve MS/MS<sup>n</sup> functionality with higher energy DC acceleration ion fragmentation at each ion  $m/z$  selection and fragmentation step. Alternatively, multiple quadrupole ion guide assembly 8 can be configured to conduct resonant frequency excitation fragmentation or combinations of both CID fragmentation techniques during an MS/MS<sup>n</sup> experiment to optimize performance for a given mass analysis. One example of a MS/MS<sup>n</sup> experiment conducted with DC acceleration CID ion fragmentation using the multiple quadrupole ion guide TOF hybrid diagrammed in Figure 1 is described below.

1. Segment 1 of quadrupole assembly 60 is operated in RF only non mass selection mode with ions being transferred into segment 2 with no fragmentation.
2. Segment 2 of quadrupole assembly 60 is operated in trapping or non trapping mass to charge selection mode and the resulting ion population is accelerated through quadrupole 61 and into quadrupole assembly 62 with sufficient kinetic energy to cause CID fragmentation.
3. Quadrupole ion guide 62 is operated in trapping mass to charge selection mode and a selected  $m/z$  range of first generation fragment ions is collected in quadrupole 62 with little or no ion gating into pulsing region 37. After collecting selected  $m/z$  first generation fragment ions for a specified time period or with occasional TOF monitoring of the ion population in quadrupole 62 to avoid saturation, the primary ion beam is prevented from entering segment 1 quadrupole assembly 60 by decreasing the potential on capillary exit lens 112 relative to the potential applied to skimmer 26. Ions exiting capillary 23 are prevented from passing through skimmer opening 27 due to the retarding electric field applied in the capillary to skimmer region.
4. Ions trapped in quadrupole ion guide 62 are then DC accelerated in the reverse direction through quadrupole ion guide 61 and into segment 2 of quadrupole assembly 60 by applying the appropriate relative DC offset potentials to the rods of segment 2, quadrupole 61 and quadrupole 62 to cause CID fragmentation of ions accelerated into segment 2. Ions accelerated in the reverse direction into segment 2

are prevented from entering segment 1 by increasing the relative DC bias potentials of segments 1 and 2. If a short MS/MS<sup>n</sup> analysis time is required, ions may be prevented from entering segment 1 to decrease the time required to empty segment 2 of ions at each MS/MS step. Alternatively ions may be allowed to enter segment 1 as an extension of segment 2 to increase the segment 1 volume. Ions are prevented from exiting segment 1 in the reverse direction through entrance end 9 by applying a DC retarding field between skimmer 26 and the poles of segment 1. Collisions with the neutral gas molecules from the free jet expansion continuing to enter second vacuum stage 72 through skimmer aperture 27, serve to damp the reverse direction axial trajectories of ions and prevents trapped ions from being lost through entrance end 9 of quadrupole assembly 60. The potentials applied to the rods of segment 2 and segment 1 just prior to receiving the ion population from quadrupole 62 are switched such that segments 1 and 2 are operated in ion m/z selection mode.

5. A selected m/z range of second generation fragment ions is collected in segment 2 of quadrupole assembly 60. The resulting population of second generation fragment ions is re-accelerated through quadrupole ion guide 61 and into quadrupole ion guide 62 with sufficient kinetic energy to cause CID fragmentation of the selected second generation ions.
6. Quadrupole ion guide 62 is again operated in ion trapping mode. If the experiment is to end at third generation ions, the resulting ion population in quadrupole 62 is TOF mass analyzed. If n generation product ions beyond MS/MS<sup>3</sup> are required, step 4 or steps 4 and 5 are repeated to produce MS/MS<sup>n</sup> generation fragment or product ions and so on. The trapped ion population can be sampled at each MS/MS step and TOF mass analyzed consuming only a small portion of the trapped ion population. TOF mass analysis is conducted after the last MS/MS<sup>nth</sup> step until the entire ion population is emptied from quadrupole 62 of multiple quadrupole ion guide assembly 8.
7. The voltage applied to capillary exit lens 112 14 is raised to allow ions in the primary ion beam to again pass through skimmer aperture 27 and into segmented 1 of quadrupole ion guide assembly 60 entrance end 9.
8. Sequence steps 1 through 7 are repeated. Any number of MS/MS<sup>n</sup> steps can be configured in this manner with TOF mass analysis.

Another example of MS/MS<sup>n</sup> analysis utilizing a mixture of resonant frequency excitation fragmentation and DC ion acceleration CID fragmentation is described below with non-continuous primary ion beam operation.

1. Operate segment 1 of quadrupole assembly 60 in non m/z selection RF only mode to pass ions into segment 2 without CID fragmentation.
2. Segment 2 is operated in mass selection mode with trapping or non trapping, passing selected m/z ions through quadrupole ion guide 61 and into quadrupole ion guide 62 with no DC acceleration fragmentation.
3. Quadrupole assembly 62 is operated in trapping mode with resonant frequency excitation fragmentation of the m/z selected parent ions. A supplemental set of resonant frequencies is simultaneously applied to reject undesired first generation fragment ions while retaining selected first generation fragment m/z value ions. The internal energy of the m/z selected first generation fragment ions does increase

in quadrupole ion guide 62 during parent ion CID fragmentation. First generation  $m/z$  selected fragment ions are accumulated in quadrupole 62 for a set time period or until a desired ion population density is reached, checked by short duration TOF mass analysis.

4. When quadrupole ion guide 62 has been filled to the desired ion density level, the primary ion beam is prevented from passing through skimmer aperture 27 by lowering the potential applied to capillary exit electrode 112.
5. The selected first generation fragmentation ions are accelerated in the reverse direction from quadrupole ion guide 62 through quadrupole ion guide 61 and into segment 2 of quadrupole ion guide assembly 60 with sufficient kinetic energy to cause CID fragmentation.
6. Prior to receiving the first generation ions and second generation fragment ions, the potentials applied to the poles of segment 2 are switched to operate in mass to charge selection mode for  $m/z$  selection of second generation fragment ions.
7. If further MS/MS analytical sequences are desired, steps 2 through 6 can be repeated. If no additional MS/MS steps are desired TOF mass analysis can be performed on the entire ion population trapped in segment 2 of quadrupole assembly 60 by transferring the ions without further fragmentation through quadrupole assemblies 61 and 62.
8. When TOF mass analysis is completed and multiple quadrupole ion guide assembly 8 has been emptied, the primary ion beam is again allowed to pass through skimmer aperture 27 and into segment 1 of quadrupole assembly 60. Steps 1 through 7 can be repeated to continue data acquisition with  $MS/MS^n$  analysis.

As is described in U.S. patent application 08/694,542 higher energy CID fragmentation can be achieved by accelerating ions back into quadrupole ion guide 62 from exit end 11 configured in the low pressure region of third vacuum pumping stage 73. Ions gated into the gap between lenses 33 and 34 are raised in potential by rapidly increasing the voltage applied to lenses 33 and 34. The potential applied to lens 33 is then decreased to accelerate ions back into multiple quadrupole ion guide assembly 8. The reverse direction DC accelerated ions impact the background gas in multiple quadrupole ion guide assembly 8 as they traverse the length of multiple quadrupole assembly 8 or individual quadrupole assemblies 62, 61 and 60. In a similar manner, quadrupole ion guide 61 or a combination quadrupole ion guides 61 and 62 can be used to reverse accelerate ions into segment 2 of quadrupole assembly 60 in a repetitive manner to rapidly increase the internal energy of an ion population. Ion acceleration from quadrupole ion guide assembly 61, however, occurs in the presence of background collision gas so the ion terminal velocities achieved may be lower than the velocities attained by reverse accelerating ions from the collision free region at ion guide exit end 11. Unlike a three dimensional ion trap or FTMS mass analyzers that can be operated  $MS/MS^n$  mass analysis mode, the multiple quadrupole ion guide TOF hybrid shown in Figure 1 can deliver a broader range of collisional energies to achieve ion fragmentation at each MS/MS step. The control of  $MS/MS^n$  function sequences is simplified by preprogrammed software functions that calculate the resonant frequency waveforms and control the RF, DC potentials applied to each segment and quadrupole assembly. Software directed controller 80 as diagrammed in Figure 2 sends waveform, amplitude, switch timing and other control information through control connections 81, 77, 78, 79, and 82 to DC, RF, SF and +/-DC power supplies and switching units 66, 63, 64, 65 and 67 respectively. Outputs connections 85, 86, 68, 69, 70, 87, 75, 76, 88 and 84 apply the appropriate potentials to the capillary exit

lens 112, skimmer 26, the rods of multiple quadrupole assembly 8, exit lenses 33, 34 and 35, and TOF pulsing lenses 41 and 42 respectively.

Rapid switching of DC offset potentials can be achieved by switching between two individual DC power supplies set at the appropriate potentials. The poles of each segment or quadrupole assembly can be connected to a set of +/- DC power supplies and waveform generators through switches. The primary RF applied to the poles of each quadrupole assembly through capacitive coupling directly from individual RF supplies configured in power supply units 63, 64 and 65. The +/- DC potentials can be added after the RF coupling capacitor and the resonant frequency AC waveform can be inductively coupled into the RF connections to appropriate poles of each segment of each quadrupole assembly. Alternatively, the resonant frequency AC waveform can be capacitively added to at least two poles of each segment of each quadrupole assembly. The state of each switch can be controlled by controller 80 from a computer program that can synchronously change the status all switches required to achieve a change of instrument state. RF, SF and DC power supply amplitudes can be set through interfaces such as Digital to Analog converters using the same computer control program.

With such a computer controlled system, MS/MS<sup>n</sup> experimental sequences are achieved by programming specific sets of switch, control signal and delay patterns. Control sequences can be user selected before initiating a data acquisition run and state changes can be programmed to occur during the run based on preset values or based on the data received. Data dependent software control decisions may be used for example to select and fragment the ion species comprising the largest peak in a parent mass spectrum. The ions species that have resulted in the largest amplitude parent peak being detected for a given mass spectrum are then m/z selected and subsequently fragmented in a preprogrammed data dependent automated software control sequence.

Quadrupole ion guide assembly 61 of multiple quadrupole assembly 8 serves to decouple quadrupole ion guides 60 and 62 both electrically and functionally. Ions can be trapped in segment 2 of quadrupole assembly 60 and released when the DC offset potentials applied to poles 3 of quadrupole ion guide 61 are increased to trap ions and lowered to pass ions from segment 2 into quadrupole ion guide 61. Multiple quadrupole assembly 8 can be constructed with an increased number of segments per quadrupole assembly or with an increased number of quadrupole assemblies to achieve greater instrument flexibility resulting in a greater range of analytical capability. Instrument flexibility and to some extent complexity can be increased to achieve additional functional capability by increasing the number of quadrupole assemblies and segments per quadrupole multiple quadrupole ion guide assembly 160 configured in hybrid quadrupole TOF 170 as daigrammed in Figure 4. Multiple quadrupole ion guide assembly 160 comprises four quadrupole assemblies 161 through 164. Two segment quadrupole assembly 161 includes analytical segment 165 and exit segment 166. Two segment quadrupole assembly 162 comprises analytical segment 167 and exit segment 168. Single segment quadrupole assembly 163 comprises segment 169 and four segment quadrupole assembly 164 comprises segments 170 through 173. The rods of each of the four quadrupole assemblies are connected to four independent RF supplies whose output RF waveforms have common frequency and phase. The rods of each of the four quadrupole assemblies are connected to independent resonant or secular frequency composite waveform supplies. The rods of each segment of each quadrupole assembly are connected to independent DC offset or +/- DC voltage supplies. Alternatively, to achieve a reduction in system cost and complexity with some reduction in analytical capability, a common RF



supply can be connected to all segments of all quadrupole assemblies of multiple quadrupole assembly 160. Care must be taken to decouple the electrical reactance when changing DC and SF potential to individual quadrupole segments during operation when a common RF supply is used. The inadvertent coupling of a rapidly switched DC potential into the RF potential can result in rapid and unwanted ion ejection from the effected quadrupole volume. Auxiliary background gas is added through channel 178 into second vacuum pumping stage 198 to modify the background gas composition in multiple quadrupole assembly 160. Valve 199 controls the auxiliary gas flow rate through channel 178 into vacuum stage 198. Helium can be added to reduce the mass of the collision gas, argon can be added to increase the mass of the collision gas or a reactant gas can be added to study ion to neutral gas phase reactions. Each adjacent segment of each quadrupole assembly and each adjacent quadrupole assembly is electrically insulated to isolate different electrical potentials applied to the rods or poles of each adjacent segment. Quadrupole assemblies 161, 162, 163 and 164 are sequentially configured along a common centerline. Multiple quadrupole assembly 160 is diagrammed in a linear configuration. Alternatively, multiple quadrupole assembly 160 can be configured with quadrupole assemblies comprising curved rods or poles.

Effectively multiple a third independent quadrupole assembly 161 has been added to multiple quadrupole assembly 160 when compared to the configuration of multiple quadrupole assembly 8 diagrammed in Figure 1. The additional quadrupole assembly 161 configured in the higher background pressure region of vacuum pumping stage 198 enables the conducting of an independent mass selection and/or fragmentation step with trapping of ions. Ions can be independently trapped in and released from quadrupole assemblies 161, 162 163 and 164 in multiple quadrupole assembly 160. The individual DC offset potential applied to the poles of segment 166 of quadrupole assembly 161 can be set to trap ions in segment 165 or release ions from segment 165 into segment 167 of quadrupole assembly 162. Mass to charge selection and DC acceleration and resonant frequency excitation CID ion fragmentation can be conducted in quadrupole assemblies 161, 162 and 164. Ions can be transferred between quadrupole ion guide assemblies in the forward and reverse directions by applying the appropriate DC offset potentials to specific segments of each quadrupole ion guide assembly. Exit segment 168 and two entrance segments 170 and 171 have been added to quadrupole assemblies 162 and 164 respectively. These added segments in conjunction with quadrupole assembly 163 provide a five step ion acceleration junction between quadrupole assemblies 162 and 164. Higher energy DC acceleration CID ion fragmentation can be achieved, particularly in higher background pressures, using a longer acceleration path provided by the added quadrupole segments. Multiple passes can also be made through the five step junction to increase ion internal energy leading to fragmentation.

The addition of a third quadrupole assembly 161 to multiple quadrupole assembly 160 in hybrid TOF 170 increases the range of analytical functions that can be conducted when compared to the hybrid TOF mass analyzer as diagrammed in Figure 1. Hybrid TOF 170 can be used to conduct  $MS/MS^n$  analysis functions that are not possible using the hybrid TOF mass analyzer as diagrammed in Figure 1, triple quadrupoles or three dimensional ion trap mass analyzers. An example of a new  $MS/MS^2$  functional sequence with a continuous ion beam and DC acceleration CID fragmentation for each  $MS/MS$  step is given below using Hybrid TOF 170.

1. Quadrupole assembly 161 is operated in mass to charge selection mode with or without repetitive ion trapping and release.

2. Parent ions mass to charge selected in quadrupole assembly 161 are accelerated into quadrupole assembly 162 with sufficient kinetic energy to cause DC acceleration CID ion fragmentation.
3. Quadrupole assembly 162 is operated in mass to charge selection mode, selecting at least one first generation fragment ion species with or without repetitive ion trapping and release.
4. First generation fragment ions mass to charge selected in quadrupole assembly 162 are accelerated through quadrupole assembly 163 and into quadrupole assembly 164 with sufficient kinetic energy to cause DC acceleration CID ion fragmentation. Quadrupole assembly 164 is operated in RF only ion trap and release mode trapping second generation fragment ions.
5. Second generation fragment ions are transferred from quadrupole ion guide 164 into pulsing region 175 where they are pulsed into TOF drift region 176 and mass to charge analyzed.

Segment 173 has been added at exit end 174 of quadrupole ion guide assembly 164 to serve as an alternative means to trap ions in quadrupole ion guide 164 and gate ions from quadrupole 164 into TOF pulsing region 175. Ions are trapped in quadrupole assembly 164 by raising the DC offset potential applied to the rods of segment 173. Trapping with DC offset potentials applied to the poles of segment 173 compared with using a DC retarding potential applied to lens 179 reduces any defocusing effects which may occur due to fringing field effects occurring at exit end 174. Segment 173 can be operated primarily in RF only ion transfer mode to reduce or minimize asymmetric DC fringing field effects that may exist at exit end 174 of quadrupole ion guide 164. Segment 173 can be configured to work in conjunction with exit lens 179 or in place of exit lens 179 for ion trapping or reverse ion acceleration functions. As is apparent to one skilled in the art, several unique analytical functional sequences are possible in addition to the example given above with four quadrupole ion guide assembly hybrid TOF 170 as diagrammed in Figure 4. Quadrupole assemblies 161, 162 and 164 configured in higher background pressure region 171 can be operated independently in mass to charge selection mode and/or resonant frequency excitation CID ion fragmentation modes. Quadrupole assemblies 161, 162, 163 and 164 can be operated in conjunction with one another to achieve DC acceleration CID ion fragmentation. A wide range of functions can be conducted to achieve MS/MS<sup>n</sup> mass analysis using hybrid quadrupole TOF 170 for a given analytical application.

An alternative embodiment to API source hybrid quadrupole TOF 170 is diagrammed in Figure 5. Referring to Figure 5, multiple quadrupole assembly 180 configured in hybrid quadrupole TOF 194 comprises individual quadrupole assemblies 181, 182 and 183 separated with electrostatic lenses 192 and 193. Electrostatic lens 192 is configured in the junction between quadrupole assemblies 181 and 182 and Electrostatic lens 193 is configured in the junction between quadrupole assemblies 182 and 183. Electrostatic lens 192 replaces quadrupole assembly 163 in multiple quadrupole assembly 160 as diagrammed in Figure 4. Electrostatic lenses 192 and 193, connected to DC power supplies, allow trapping and release of ions from adjacent quadrupole assemblies. Ions can still be moved in the forward and reverse directions between quadrupole assemblies in multiple quadrupole assembly 180, however, the presence of DC lenses in the interquadrupole junctions causes some distortion of the applied RF radial trapping field and the resonant AC field at ends of adjacent quadrupoles. This RF and AC field distortion plus

the reduced transmission areas of orifices 195 and 196 in lenses 192 and 193 respectively can result in ion transmission losses between quadrupole assemblies reducing sensitivity. The tradeoff in performance is balanced against a potential reduction in cost from the elimination of RF power supplies while retaining the ability to trap and release ions independently in quadrupole ion guide assemblies 181, 182 and 183. Alternatively, electrostatic lenses 192 and/or 193 can be configured as multiple lens sets to allow electrostatic focusing or acceleration of ions as they traverse the junctions between quadrupole ion guide assemblies. Three individual sets of RF, +/- DC and resonant frequency waveform power supplies apply electrical potentials independently to the rods of quadrupole assemblies 181, 182 and 183. Separate DC offset potentials can be applied independently to each segment 184, 185, 186, 187, 188, 189, 190 and 191 of multiple quadrupole assembly 180. Quadrupole assemblies 181 and 182 and a portion of quadrupole assembly 183 are configured in higher background pressure vacuum stage 197. Independent mass to charge selection and resonant frequency excitation CID ion fragmentation can be conducted in quadrupole assemblies 181, 182 and 183. DC acceleration CID ion fragmentation can be achieved by ion acceleration between segments within quadrupole assemblies or by accelerating ions between quadrupole assemblies 181 and 182 and 182 and 183 in the forward or reverse directions. Alternatively, ions can be accelerated in reverse direction from the exit end of quadrupole 183 into quadrupole 183 to achieve DC acceleration CID ion fragmentation. As is apparent from the description given above for the hybrid quadrupole TOF embodiments as diagrammed in Figures 1 and 4, API source hybrid quadrupole TOF 194 can be operated to conduct a range of MS/MS<sup>n</sup> mass analysis functions with the option of using different methods to achieve mass to charge selection and ion fragmentation in each MS/MS step. Hybrid quadrupole TOF 194 can be used to perform triple quadrupole and three dimensional quadrupole ion trap mass analysis and is capable of performing mass analysis functions not possible using either triple quadrupoles or three dimensional ion traps.

Less complex single or multiple quadrupole assemblies can be configured in hybrid quadrupole TOF apparatus to lower instrument cost and reduce operating complexity. Flexibility in operation and analytical capability may be reduced, depending on the application desired, as the multiple quadrupole configuration is simplified. Quadrupole ion guide assembly 61 of multiple quadrupole assembly 8 serves to decouple quadrupole ion guides 60 and 62 both electrically and functionally. Ions can be trapped in segment 2 of quadrupole assembly 60 and released when the DC offset potentials applied to poles 3 of quadrupole ion guide 61 are increased to trap ions and lowered to pass ions from segment 2 into quadrupole ion guide 61. Figure 6 shows an alternative embodiment of a hybrid multiple quadrupole ion guide TOF instrument 215 comprising electrospray ion source 212, four vacuum pumping stages 208, 209, 210 and 211, multiple quadrupole assembly 204 and TOF mass analyzer 216. Multiple ion guide 204 comprises individual quadrupole assemblies 201, 202 and 203 positioned along common centerline 205 having individual RF, +/-DC and resonant waveform supplies allowing the performing of independent mass selection and ion fragmentation functions with each quadrupole assembly. In one aspect of the invention, all three RF power supplies are operated with a common frequency and phase output. Common frequency and phase are applied to axially aligned rods of each quadrupole assembly 201, 202 and 203 in multiple quadrupole assembly 204 to maximize ion transfer efficiency between quadrupole assemblies. Quadrupole assembly 203 extends continuously from higher background pressure vacuum pumping stage 209 into lower background pressure vacuum stage 210. Examples of combinations mass to charge selection and in fragmentation steps

conducted multiple quadrupole ion guides with TOF mass analysis given above can be applied to multiple quadrupole assembly 204 configured in hybrid TOF 215.

Alternatively, individual quadrupole assemblies 201 and 202 can be configured as two segments of a quadrupole assembly where the RF potentials applied to the rods of both segments originates from a common RF power supply. In this alternative embodiment, multiple quadrupole assembly 204 comprises two quadrupole assemblies, the first quadrupole assembly comprising segments 201 and 202 and the second quadrupole 203 assembly comprises a single segment. Independent +/-DC (including offset DC) and resonant frequency waveforms are applied to the rods of quadrupole sections and assemblies 201, 202 and 203 allowing the performing of independent mass to charge selection and ion fragmentation functions in each quadrupole section or assembly. Comparing this alternative embodiment with multiple quadrupole assembly 8 as diagrammed Figure 1, quadrupole assembly 61 has been removed in dual quadrupole assembly 204. The removal of quadrupole assembly 62 segmented ion guide 8 simplifies operational sequences and reduces cost of electronic components. Many  $MS/MS^n$  sequences described using the embodiment shown in Figure 1 can be run with the dual quadrupole assembly 202 as diagrammed in Figure 2. By setting the appropriate relative DC offset potentials between quadrupole segments and/or assemblies 201, 202 and 203, DC acceleration CID ion fragmentation can occur by accelerating ions in the forward or reverse directions between quadrupole segments or individual quadrupole assemblies through junctions 206 and/or 207 or in the reverse direction from the exit end of quadrupole 203. The background pressure in vacuum second stage 209 is maintained above 0.1 millitorr to allow collisional damping of stable trajectory ion energies and to enable CID fragmentation of ions in each multipole ion guide section or assembly. The local pressure at entrance end 213 of segment or quadrupole 201 is higher due to the free jet expansion and aids in increasing the ion guide capture efficiency at entrance 213 of multiple quadrupole assembly 204. Elimination of an independent quadrupole assembly 61 or segment in the junction between segments 202 and quadrupole 203 results in reduced flexibility in simultaneously trapping different ion populations ions in both segment 202 and quadrupole 203. This reduced functionality simplifies instrument operation and cost by reducing variables and components. Combining aspects of the invention shown Figures 1 through 5, alternative embodiments of the invention can be configured into hybrid TOF 215. For example, electrostatic lenses can be included in junctions 206 and 207 to allow trapping of ions in segments or quadrupoles or the transfer of ions across junctions 206 and 207. Electrostatic also serve to isolate capacitive coupling of electric fields between quadrupole assemblies. Multiple quadrupole assembly 204 can also operated as a three segment ion guide with RF applied to the poles of all three segments originating from one power supply. Several  $MS/MS^n$  mass analysis functions can be conducted in this single RF supply embodiment with a reduced electrical component complexity and cost.

The configuration of the guide assembly configured in a hybrid quadrupole TOF can be further simplified while retaining the ability of performing  $MS/MS^n$  analysis functions. An alternative embodiment of the invention is diagrammed in Figure 7 in which three segment quadrupole ion guide 408 is configured in a hybrid API TOF mass analyzer. In the simplest embodiment, RF potential is applied to the rods of the three segments 401, 402 and 403 from a common RF power supply, with separate DC offset applied to each segment. Individual +/-DC and resonant waveforms can be applied to the rods of segments 401 and 402 to conduct mass to charge selection and resonant frequency excitation CID fragmentation of selected

ions. Three segment multipole ion guide 408 extends continuously from higher background pressure vacuum stage 411 into lower background pressure vacuum stage 412. Segment 402 can be operated in RF only mode to transfer ions into TOF pulsing region 415 or as a two dimensional trap configured with full MS/MS<sup>n</sup> function capability when coupled with TOF mass analysis as is described in U.S. Patent Application Number 08/694,542. The embodiment in Figure 4 includes two additional segments configured in quadrupole assembly 408 not described in U.S. patent application 08/694/542. Segments 401 and 403 can be operated in modes that serve to decouple or minimize the fringing field effects of potentials applied to segment 408 during mass to charge selection and ion fragmentation operating modes. Minimizing the fringing field effects allow optimization of the trajectories of ions entering or exiting quadrupole ion guide 408 at entrance and exit ends 416 and 417 respectively. For example segment 401 can be operated in RF only mode to efficiently transfer ions from entrance region 416 into segment 408. The kinetic energies and trajectories of ions entering multipole ion guide 408 at entrance end 416 are damped by the collisional interaction with the background gas. Ions traversing segment 401 enter segment 408 closer to centerline 418 where the defocusing effects of DC fringing fields will have minimum effect on ion transmission efficiency. The DC offset potentials applied to segment 403 can be switched to trap ions in segment 402 or gate ions from segment 402 into TOF pulsing region 415. Ions traversing pulsing region 415 are pulsed into TOF drift region 414 and mass analyzed. A linear TOF flight tube geometry is shown in Figure 7 as an alternative embodiment to a TOF flight tube geometry which includes an ion reflector geometry.

Segment 403 operating in RF only mode provides consistent ion trajectories for ions traversing from multipole ion guide exit region 417 into TOF pulsing region 415 by shielding non uniform fringing fields at the exit end of segment 2 which can occur during different operating modes of segment 402. Segment 401 can also be operated in m/z selection and/or fragmentation mode and parent or product ions can be transferred forward or in reverse between segments 401 and 402. Consequently, ions can be fragmented with DC ion acceleration between segments 401 and 402 complementing resonant frequency CID functions described in previous embodiments and in U.S. Patent Application Number 08/694,542. Ions traversing segment 403 may be accelerating back into segment 402 to cause CID ion fragmentation in that portion of segment 402 which extends into vacuum stage 411. Pulsing ions in the reverse direction from segment 403 into 402 can be accomplished by switching the DC potentials applied to the poles of segment 403 and lens 419 in a synchronous manner to initially raise the ion energy of the ions in exit region 417 and then accelerate the ions in reverse direction along quadrupole centerline 418 into segment 402. Some DC field penetration into segment 403 from lens 419 and the poles of segment 402 will occur with DC voltage differences applied between the two elements to aid accelerating the ions from segment 403 into 402. The embodiment diagrammed in Figure 4 allows full MS/MS<sup>n</sup> functionality in a cost effective configuration with some tradeoffs in functional flexibility due to the reduced number of multipole ion guide segments or individual quadrupole assemblies operated in a higher pressure vacuum region.

An alternative embodiment of a three segment multipole ion guide diagrammed in Figure 8 in which segmented multipole ion guide 448 is configured to extend into first vacuum pumping stage 450. Ions produced in Electrospray ion source 452 move into first vacuum pumping stage 450 through capillary 453. Ions exiting capillary 453 at exit end 454, enter first multipole ion guide segment 441 where they are radially confined by the RF fields applied to

the poles on segment 441. Ions with  $m/z$  values which fall within the stability window determined by the electric fields applied to the poles of segment 441 move through segment 441 and are transferred into segment 442.  $MS/MS^n$  functions with TOF mass to charge analysis can be achieved using techniques similar to those described for the three segment ion guide shown in Figure 7. Alternatives to segmented ion guide 448 may include extending segment 442 into vacuum stage 450. Additional multipole ion guide segments can be added to that portion of multipole ion guide 448 which extends into vacuum stage 454. This configuration allows mass to charge selection and ion fragmentation functions at higher background pressures which may be preferable to lower pressure operation for some analysis applications. Additional configurations of the multiple quadrupole or multiple segment quadrupole assembly configured in a hybrid quadrupole TOF mass analyzer are diagrammed in Figures 9 through 11.

Independent quadrupole or segmented multipole ion guide assembly 502 diagrammed in Figure 9 extends into TOF pulsing region 507. Ions traversing the length of multipole ion guide 508 pass through independent quadrupole assemblies or segments 501, 502 and 503 and are transferred into quadrupole or segment 507. The relative DC voltages applied to the poles of segments 503 and 504 and lens 506 trap ions in quadrupole assembly 504. Ions trapped in segment 504 are pulsed into TOF drift region 510 by cutting off the RF voltage component and applying an asymmetric DC potential to the poles of segment 504 to accelerate ions radially through the gap between two poles as described by Franzen in U.S. Patent Number 5,763,878, which is fully incorporated herein by reference. In an alternative configuration, Ijames, C.F. Proceedings of the 44th ASMS Conference on Mass Spectrometry and Ion Physics, Page 795, 1996, describes replacing trapping lens 506 with a quadrupole ion guide with lateral ion extraction of trapped ions from quadrupole 504 into the TOF drift region.

Full  $MS/MS^n$  functions with TOF mass to charge analysis can be achieved using the hybrid TOF embodiment shown in Figure 9. Individual quadrupole assemblies or segments 501, 502 and 503 can be operated individually or in complementary fashion to achieve ion mass to charge selection and/or ion CID fragmentation of ions prior to TOF mass to charge analysis. Similar to embodiments described above, multiple quadrupole assembly 508 is configured with four independent sets of RF, +/DC and resonant frequency waveform power supplies applying different potentials to the rods of individual quadrupole assemblies 501, 502, 503 and 504 with common RF frequency and phase. Each quadrupole assembly 501, 502 and 503 located in higher pressure vacuum stage 512 can be independently cooperatively operated in mass to charge selection and/or ion fragmentation modes to conduct  $MS/MS$  steps of  $MS/MS^n$  mass analysis functions with TOF mass to charge analysis. Quadrupole 507 is configured in a low pressure vacuum region where little or no ion collisions occur with the neutral background gas. Consequently, no collisional damping can occur for ions trapped in quadrupole assembly 504 prior to pulsing laterally into TOF drift region 510.

The ions trapped in quadrupole assembly 504 prior to pulsing into TOF drift region 510 may be traveling in either direction axially along the length of quadrupole 504. The axial trajectory of ions moving in opposite directions in quadrupole 504 cannot be simultaneously directed by steering lenses 511 to impact on the TOF detector. To increase the number of ions which have the required trajectory to impact the detector in the TOF tube, ions must be accelerated laterally from quadrupole assembly 504 during the initial first pass of ions that

enter quadrupole ion guide 504 or ions must be transferred into quadrupole 504 with very low axial kinetic energy. The latter has the disadvantage that the pulsing region fill time may be quite long resulting in the reduction of the TOF pulse rate. Undamped radial ion motion in quadrupole assembly 504 due to the RF field contributes to the spatial and energy spread of ions accelerated laterally into TOF drift region 510. An additional constraint that must be considered when operating with a two dimensional trap configured in the TOF pulsing region is that a multichannel plate detector commonly used in TOF analyzers has a limited instantaneous charge depletion linear dynamic range response, typically on the order of 100. If too many ions of like  $m/z$  value arrive at the detector within a 2 nanosecond time window, the detector output may reach saturation resulting in signal amplitude distortion. Reducing ion accumulation time in quadrupole 504 prior to pulsing the trapped ions into TOF drift region 510 can help to avoid detector saturation. The potentials applied to steering lens set 511 can be optimized maximize the number of ions pulsed from quadrupole 504 that impact on the TOF detector.

An alternative embodiment of a hybrid API source multipole ion guide TOF is diagrammed in Figure 10. Referring to Figure 10, an additional multipole ion guide 610 has been configured between segmented quadrupole ion guide assembly 608 and TOF pulsing region 611. Multipole ion guide 610 can be operated as a collision cell when gas is added to collision cell assembly 612 surrounded by partition 614 or, configured as a quadrupole ion guide, can also be operated in mass to charge selection mode. Segments 601, 602 and 603 comprising quadrupole ion guide 608 can be operated individually or collectively in mass to charge selection and/or CID ion fragmentation modes to achieve  $MS/MS^n$  functions with TOF mass to charge analysis. Each segment of multipole ion guide 608 can be operated in single pass or ion trapping mode. In addition, ions can be mass to charge selected with DC acceleration or resonant frequency excitation CID ion fragmentation in multipole ion guide 610. Multipole ion guide 608 extends continuously from higher background pressure vacuum stage 613 into lower pressure vacuum stage 615 where ions exiting from segment 603 are not subjected to collisional scattering from collisions with neutral background gas molecules. Ion transfer efficiency into multipole ion guide 610 is aided by the collisional damping of ions as they traverse segment 601 and the portion of segment 602 positioned in vacuum pumping stage 613. The configuration of separate collision cell assembly 612 comprising multipole ion guide 610 allows the introduction of a collision or reactive background gas that has the same or different composition from the background gas present in second vacuum stage 613. The hybrid TOF embodiment shown in Figure 10 allows studies of gas phase ion neutral reactions or the use of different gases for CID fragmentation of ions with full  $MS/MS^n$  mass analysis capability. Multipole ion guide 610 can be operated in single pass or ion trap and release mode with the gating of ions into TOF pulsing region 611. An additional RF multipole ion guide may be configured in vacuum stage 615 between multipole ion guide 610 configured in a collision cell and TOF pulsing region 611 to reduce the background pressure between CID region 612 and fourth vacuum stage 618 which is maintained at low background pressure. Multipole ion guide 608 may also be configured to extend into poles of ion guide 610 to improve ion transmission efficiency as is described in U.S. Patent Application Serial Number 60/017,619 which is incorporated herein by reference. The dual multipole ion guide embodiment shown in Figure 10 allows specialized operating modes such as employing two separate collision gases in an  $MS/MS$  or  $MS/MS^n$  mass analysis sequence. The hybrid TOF embodiment as diagrammed in Figure 10 also allows the conducting of ion mass to mass to charge selection and/or CID ion fragmentation functions in either quadrupole ion guide

assemblies 608 or 610 that may be configured with different cross sections and have different +/- DC and RF frequency, phase and amplitude potentials applied to rods of each quadrupole assembly. Ions can be accelerated in the forward and reverse directions between quadrupole assemblies 608 and 610 to cause DC acceleration CID ion fragmentation.

Figure 11 shows an alternative embodiment for a multipole ion guide hybrid TOF mass analyzer that can be operated in MS/MS<sup>n</sup> analysis mode. Segmented quadrupole ion guide assembly 708, configured with segments 701, 702 and 703, is positioned in higher background pressure vacuum second vacuum stage 710. A second quadrupole ion guide assembly 704 located in lower background pressure vacuum stage 711 is surrounded by gas partition 713. Gas partition 713 allows the addition of collision gas into region 713 to raise the pressure in region 713 above the background pressure in vacuum stage 711 when it is desirable to operate ion guide 704 as a collision cell. A third multipole ion guide 714 is positioned in vacuum stage 711 to efficiently transfer ions from multipole ion guide 704 into pulsing region 712 allowing sufficient vacuum pumping between higher pressure collision region 713 and lower pressure TOF pulsing region 712. Quadrupole ion guide 704 may be operated in single pass or ion trapping mode with gating of ions into TOF pulsing region 712. Positioning quadrupole ion guide assemblies 708 and 704 in separate vacuum stages allows increased flexibility in configuring multipole ion guide geometries particularly for quadrupole assembly 708. Multipole ion guides which extend into more than one vacuum stage are configured with relatively small inner diameters (small  $r_0$ ) to minimize the neutral gas conductance from one vacuum stage to the next. Minimizing gas conductance reduces vacuum pumping costs for a given background target pressure. The poles of multipole ion guide assemblies 708, 704 and 714 begin and end vacuum stages 710 and 711 respectively so there are no vacuum pumping constraints imposed on any multipole ion guide geometry. The inner radius ( $r_0$ ) of ion guide 708, 704 or 714 are not constrained due to vacuum pumping requirements in the embodiment shown in Figure 7.

Analogous to previously described embodiments, the background pressure in vacuum stage 710 is maintained sufficiently high to insure that collisions between background gas and ions occur as ions traverse the length of quadrupole assembly 708. The background pressure in vacuum stage 710 allows CID ion fragmentation of ions traversing multipole ion guide 708 using resonant frequency excitation or intersegment DC ion acceleration techniques. Each segment in multipole ion guide 708 can be operated independently or in conjunction with other segments in  $m/z$  selection or CID ion fragmentation operating modes. Voltages applied to vacuum partition and electrostatic lens 707 can be set to pass ions from segment 703 into multipole ion guide 704 or can be set to trap ions in multipole ion guide 708. Each segment in multipole ion guide 708 can be operated in trapping or nontrapping mode by setting the appropriate relative DC offset potentials to the poles of adjacent segments. Similarly multipole ion guide 704 can be operated in ion  $m/z$  selection mode with low or higher background pressure or in resonant frequency excitation CID ion fragmentation mode when collision gas is present in region 713. Ions can also be DC accelerated into multipole ion guide 704 with sufficient kinetic energy to cause CID fragmentation. Ions can be accelerated the forward or reverse directions between quadrupole or multipole ion guide assemblies 708 and 704 with sufficient energy to cause DC acceleration CID ion fragmentation. Combinations of ion  $m/z$  selection and CID ion fragmentation functions can be conducted with quadrupole ion guide assemblies 708 and 704 to achieve a variety of MS/MS<sup>n</sup> analytical



functions with TOF mass analysis. As with the collision cell embodiment 612 diagrammed in Figure 10, collision gas or reactant gas can be introduced into region 713 with a composition that is different than the composition of the background gas in vacuum stage 710. Selected ion-molecule reactions can be studied by adding the appropriate reactant gas into collision cell region 713. Reactant product ions can be mass to charge selected or fragmented in one or more steps in either quadrupole ion guide 704 or 708. The resulting ion population ultimately flowing through or trapped in multipole ion guide 704 is subsequently TOF mass analyzed.

The embodiments of the invention diagrammed in Figures 1 through 11 are some examples of configurations and operation of hybrid multiple quadrupole ion guide TOF mass analyzers where ion mass to charge selection and ion fragmentation is conducted using at least one quadrupole ion guide positioned in a higher pressure vacuum region. Multiple collisions between ions and neutral background gas molecules occur in the quadrupole ion guides configured in the higher pressure vacuum region. The invention is not limited to the specific embodiments shown and techniques described. For example, where segmented quadrupole ion guides are described, individual quadrupole ion guides may be positioned in the higher background pressure region and used to conduct independent or coordinated  $m/z$  and ion fragmentation steps in an  $MS/MS^n$  analysis. A preferred embodiment is to apply the same RF frequency and phase from different synchronized RF power supplies to individual quadrupole ion guides in an assembly. RF amplitude, +/- DC (including DC offset) and resonant frequency waveforms can be independently varied for each quadrupole ion guide in such an assembly. Alternatively, RF with different frequency and phase can be independently applied to individual quadrupole ion guides comprising an assembly. One preferred embodiment with non synchronized RF frequency and phase between quadrupole ion guides, is the configuration of an electrostatic lens in the junction between two adjacent quadrupole ion guides to minimize fringing field effects for ions traversing between ion guides.

The four vacuum pumping stage embodiment shown can be re-configured as a two, three or five stage vacuum system with  $m/z$  selection and/or CID fragmentation conducted with at least one multipole ion guides located in a higher background pressure vacuum region. Different ion sources can be configured with the hybrid multiple quadrupole ion guide TOF hybrid instrument. Even ion sources which operate in vacuum or partial vacuum can be configured with multipole ion guides operating at higher background vacuum pressures. With ion sources that operate in vacuum, gas may be added to the vacuum region containing the multipole ion guide to operate in higher pressure  $m/z$  selection and ion fragmentation modes. The invention can be applied to variations of TOF mass analyzer geometries. For example, the TOF mass analyzer may be configured with an in line pulsing region, a multiple stage or curved field ion reflector or a discrete dynode multiplier. In alternative embodiments, the portions of segmented multipole ion guides or individual multipole ion guides located in a higher pressure vacuum regions can also be configured to operate in ion transfer, ion trapping and any of the CID ion fragmentation modes described above as well as in  $m/z$  scanning or  $m/z$  selection mode or combinations of these individual operating modes. The CID ion fragmentation, ion mass to charge selection, and  $MS/MS^n$  methods described in the embodiments of the invention can be extended to alternative embodiments of the invention. In one such alternative embodiment of the invention, the last mass analysis step of any MS or  $MS/MS^n$  sequence is performed by a quadrupole ion guide.

Detector 38 as diagrammed in Figure 1 is used to detect ions prior to TOF mass analysis. One aspect of the invention is the configuration and operation of at least one or a portion of one quadrupole ion guide configured and operated in a higher pressure vacuum region where multiple collisions between ions and neutral gas molecules occur. As was described above, an important feature of multipole ion guides is that ions in stable trajectories can be released from one end of an ion guide or ion guide segment operating in single pass or ion trapping mode simultaneously while ions are entering the opposite end of the multipole ion guide or individual segment. Due to this feature, a segmented ion guide receiving a continuous ion beam can selectively release only a portion of the ions located in the ion guide into another multipole ion guide or other mass analyzer which performs mass analysis on the released ions. In this manner ions delivered in a continuous ion beam are not lost in between discrete mass analysis steps. Another aspect of the invention is the configuration of an API source with a segmented multipole ion guide positioned in a higher pressure vacuum region where the multipole ion guide may or may not be configured with additional quadrupole mass analyzers or multipole ion guide collision cells. The segmented quadrupole ion guide can be configured as an MS or MS/MS<sup>n</sup> mass analyzer with a portion of the segmented ion guide length operated in background vacuum pressures above 10<sup>-4</sup> torr. The electron multiplier ion detector configured with quadrupole mass analyzers configured according to the invention may be located and operated in a lower or higher background pressure vacuum region. Single or multiple vacuum stage segmented multipole ion guides configured as mass analyzers or as a portion of a multiple quadrupole mass analyzer operated in a higher pressure vacuum region be used to perform a wider range of MS or MS/MS<sup>n</sup> analytical functions for lower cost and instrument complexity than can be achieved conventional quadrupole mass analyzer configurations. Operating an API source quadrupole mass analyzer at higher vacuum background pressures can reduce instrument size and cost by reducing the vacuum pumping speed requirements.

Figure 14 shows an embodiment of the invention where multiple quadrupole assembly 1010 comprises four independent quadrupole ion guide assemblies configured in an API quadrupole mass analyzer. Quadrupole ion guide 1008 is configured with segments 1001 and 1002. Individual quadrupole assemblies 1003, 1004 and 1005 are configured with one segment each. Segments 1001 and 1002 and quadrupole assemblies 1008, 1003, 1004 and 1005 are configured along common centerline 1011 with electrically insulated junctions 1018, 1019, 1020 and 1021 separating each segment or quadrupole assembly respectively. Up to junction 1021 in third vacuum stage 1017, Electrospray source 1012, segmented quadrupole ion guide 1008, quadrupole assemblies 1003 and 1004 and vacuum pumping stages 1015, 1016 and 1017 are configured and can be operated similar to those common elements of the hybrid quadrupole TOF embodiment as diagrammed in Figure 1. TOF mass analyzer 40 of Figure 1 has been replaced by quadrupole assembly 1005 in the embodiment of the invention diagrammed in Figure 14.

As diagrammed in Figure 2, individual power supply units each supplying RF, +/-DC (including DC offset) and resonant frequency waveforms potentials to the rods of quadrupole assemblies 1008, 1003, 1004. An independent RF and +/-DC power supply unit also supplies potential to the rods of quadrupole assembly 1005. In a preferred embodiment of the invention, the same RF frequency and phase is applied to all aligned rods in multiple quadrupole assembly 1010 to provide maximum transfer efficiency of ions in stable trajectories between segments or quadrupole assemblies in the forward or reverse direction. Different RF amplitude, +/-DC (including DC offset) and resonant frequency waveforms can

be applied to the rods of each individual quadrupole assembly. Different DC offset and resonant frequency waveforms can be applied to different segment 1001 and 1002 of ion guide assembly 1008. Alternatively, RF potentials having different frequency and phase can be applied to individual quadrupole assemblies 1008, 1003, 1004 and 1005 during mass analysis operation. It may be preferable with non synchronized RF applied to different quadrupoles to replace quadrupole assembly 1003 with an electrostatic lens and include an electrostatic lens in junction 1021 between quadrupole assemblies 1004 and 1005. Alternatively, RF potential can be applied to the rods of segments 1001, 1002 and quadrupole ion guides 1003 and 1004 from a common RF supply.

Second vacuum stage 1016 is operated with a background maintained above of  $10^{-4}$  torr where multiple collisions occur between ions and neutral gas molecules as ions traverse the length of multiple quadrupole assembly 1010. Quadrupole ion guide assembly 1005 is configured in third vacuum stage 1017 which is maintained at a background pressure below  $10^{-4}$  torr where few collisions occur between ions and background gas molecules as ions traverse the length of quadrupole assembly 1005. Quadrupole ion guide 1005 may be operated in mass to charge scanning or selected ion monitoring mode. The embodiment shown in Figure 10 can perform all MS and MS/MS analytical functions performed by conventional triple quadrupole configurations as diagrammed in Figure 20 as well as additional MS/MS analytical functions. The four basic MS/MS triple quadrupole operating modes are listed in a previous section.

The previously listed MS/MS triple quadrupole mass analysis functions can be performed with the API multiple quadrupole embodiment shown in Figure 14 by using the following operating sequences.

1. Segment 1001 is operated in ion single pass (non trapping) RF only mode with the applied RF amplitude set to pass the desired range of m/z values. The relative DC offset potentials applied to the poles of segments 1001 and 1002 are set to transfer ions from segment 1001 into segment 1002 without DC acceleration ion fragmentation.
2. Segment 1002 is operated in single pass (non trapping) ion mass to charge selection mode. Ion mass to charge selection can be conducted using segment 1002 using the mass to charge selection techniques described for segment 2 of quadrupole assembly 60 as diagrammed in Figure 1. The RF amplitude may be modulated while applying the appropriate +/- DC potentials to the rods of segment 1002. Alternatively, RF modulation can be used with +/- DC and a resonant frequency waveform applied to the rods of segment 1002 to conduct single pass ion mass to charge selection. For MS/MS applications that require mass to charge scanning of quadrupole 1008, the same mass to charge separation techniques can be used stepping the appropriate RF and +/- DC amplitude potentials or resonant waveform m/z excitation frequency notch through the desired mass to charge range with or without RF modulation.
3. Quadrupole assemblies 1003 and 1004 are operated in RF only mode. The relative DC offset potentials applied to segment 1002 and quadrupole assemblies 1003, 1004 and 1005 are set to accelerate mass to charge selected ions from segment 1002 through quadrupole 1003 and 1004 and into quadrupole ion guide 1005 with sufficient energy to cause CID fragmentation of accelerated ions in quadrupole ion guides 1003 and 1004. The background pressure in the entrance end of quadrupole

1004 can be maintained sufficiently high to damp ion trajectories toward the centerline after ion fragmentation has occurred to produce an ion beam with low kinetic energy spread transferred into quadrupole ion guide 1005. With sufficient post fragmentation ion kinetic energy collisional damping in quadrupole 1004, the kinetic energy of ions entering quadrupole 1005 is determined by the relative DC offset potentials applied to the poles of quadrupole 1004 and 1005. Low velocity ions traversing quadrupole 1005 are exposed to more RF cycles improving mass to charge selection resolution.

4. Segment 1005 is operated in mass to charge selection mode. The ion mass to charge value selection range may be fixed in some triple quadrupole MS/MS operating modes or scanned as is required in other MS/MS operating modes. Ion mass to charge selection in quadrupole assembly 1005 can be conducted using the more conventional ramping of RF and +/- DC amplitude applied to the rods of quadrupole 1005. The m/z selection scanning ramps of segments 1002 and 1005 can be synchronized to perform neutral loss scans or monitoring of selected fragmentation events.
5. Ions passing from quadrupole ion guide 1005 through lens 1006 are accelerated into conversion dynode 1007. The resulting secondary electrons and photons are detected with electron or photomultiplier 1024. Alternatively, ions can be accelerated directly into electron multiplier 1024 and detected.

The embodiment of the invention as diagrammed in Figure 14 is capable of conducting additional analytical functions not possible with conventional triple quadrupole configurations as diagrammed in Figure 20 where the first and third analytical quadrupoles, 554 and 556 respectively, are operated in a low pressure vacuum region to minimize ion collisions with the background gas. For example non-trapping continuous ion beam MS/MS<sup>2</sup> analysis can be achieved by operating segment 1001 in mass to charge selection mode and accelerating the selected ions into segment 1002 with sufficient energy to cause DC acceleration CID fragmentation in segment 2 of quadrupole assembly 1008. Segment 1001 can be operated in static or scanning ion mass to charge selection mode. Alternatively, MS/MS<sup>2</sup> analysis can be conducted with resonant frequency excitation CID ion fragmentation of the parent ion if it is desirable to not increase the internal energy of the fragment ions. This can be achieved in scanning or non scanning modes as follows;

1. Segment 1001 is operated in single pass (non trapping) RF only mode with the applied RF amplitude set to pass the desired range of ion m/z values.
2. Segment 1002 is operated in single pass (non trapping) m/z selection mode. Ion mass to charge selection can be conducted with static single range ion m/z selection or with repetitive scanning over a range of ion mass to charge values at the desired scan speed. With resonant frequency excitation ejection mass to charge selection operation, multiple parent ion m/z values can be selected simultaneously.
3. The relative DC offset potentials applied to the rods of segment 1002 and quadrupole ion guides 1003 and 1004 are set to accelerate mass to charge selected ions through quadrupole 1003 and into quadrupole 1004 without causing DC acceleration CID ion fragmentation. Quadrupole 1004 is operated in resonant frequency excitation CID ion fragmentation mode to fragment the parent ion m/z value ions selected in segment 1002. The first generation fragment ions produced in quadrupole 1004 pass into quadrupole ion guide 1005 with the appropriate relative DC offset potentials set to optimally pass ions through quadrupole ion

- guide 1005 with maximum  $m/z$  selection resolution. The background pressure in the entrance end of quadrupole assembly 1004 is maintained sufficiently high to damp ion trajectories after fragmentation to achieve an ion beam damped radially to centerline 1011 with low energy spread. In this manner, the kinetic energy of ions entering segment 1005 is determined by the relative DC offset potentials applied to the rods of quadrupole assemblies 1004 and 1005.
4. Quadrupole ion guide 1005 is operated in mass to charge selection mode. The ion mass to charge value selection range may be fixed in some triple quadrupole MS/MS applications or scanned as is required in other applications. The ion mass to charge selection scanning ramps of segment 1002 quadrupole 1005 can be synchronized to perform neutral loss scans or monitoring of selected fragmentation events.
  5. Ions passing from quadrupole ion guide 1005 through lens 1006 are accelerated into conversion dynode 1007. The resulting secondary electrons and photons are detected with electron or photomultiplier 1024. Alternatively, ions can be accelerated directly into electron multiplier 1024 and detected.

In the preferred embodiment with common RF frequency and phase applied to all four quadrupole assemblies, ions can be transferred efficiently from quadrupole ion guide 1004 to quadrupole 1005 with low kinetic energy to achieve higher resolution mass to charge selection scanning in quadrupole 1005. Ions can be temporarily trapped in quadrupole ion guides 1008, 1003 and 1004 to increase the ion resident time. Increased ion resident time exposes ions to an increased number of RF cycles leading to improved ion mass to charge selection resolution or more efficient resonant frequency excitation CID ion fragmentation. Mass to charge selection scan speeds can be matched to the ion trapping and release rates, for example with discrete  $m/z$  value scan steps, to improve  $MS/MS^n$  performance. An electrostatic lens can be configured in junction 1021 between quadrupole assemblies 1004 and 1005. Said electrostatic lens would serve to decouple any rapidly changing RF and +/- DC potentials applied to the rods of quadrupole 1005 during mass to charge scanning from effecting the potentials applied to the rods of quadrupole assembly 1004. An added electrostatic lens would also reduce any fringing field effects in junction 1021 allowing different RF frequency, phase and amplitude potentials to be applied to the rods of quadrupoles 1004 and 1005. If a detector is used that can operate in a higher background pressure, the entire multiple quadrupole ion guide assembly 1008 can be configured in a single higher background pressure vacuum stage. Elimination of a vacuum pumping stage will reduce instrument cost, size and complexity while imposing little or no reduction in system flexibility or performance. Configuring segmented multipole ion guide 1008 in a single vacuum pumping stage eliminates any size constraint on the internal diameter to minimize neutral gas conductance between multiple vacuum pumping stages. Alternatively, multiple quadrupole ion guide assembly 1008 can also be configured to extend into first vacuum stage 1015 in a two or three vacuum stage system. Additional alternative embodiments for triple quadrupole like mass analyzers configured with a multiple quadrupole ion guide assemblies with at least one quadrupole ion guide operated in mass to charge selection mode in a higher pressure vacuum region are diagrammed in Figures 15 through 17.

Figure 15 is a diagram of an alternative embodiment of the invention in which dual quadrupole ion guide assembly 1110 is configured with an additional quadrupole ion guide assembly 1104 configured in a low background pressure vacuum stage 1117. The

configuration of quadrupole assembly 1104 in the triple quadrupole mass analyzer embodiment shown in Figure 15 is a variation of the embodiment shown in Figure 14. In the embodiment of the invention diagrammed in Figure 15 quadrupole 1104 may be configured with rods having a different cross section than the cross section geometry and dimensions of the rod assembly of multiple quadrupole assembly 1110. Multiple quadrupole assembly 1110 comprises two segment quadrupole 1108 and quadrupole assembly 1103. Segments 1101 and 1102 can be operated in mass to charge selection mode with CID fragmentation of ions in quadrupole assembly 1003 operated in RF only mode. Segments 1101 and 1102 and the entrance end of quadrupole ion guide 1103 are configured in higher background pressure vacuum pumping stage 1116. Electrostatic lens 1105 is configured in junction 1118 between quadrupole 1103 and quadrupole 1104. Lens 1103 minimizes the effects of fringing fields in junction 1118 created by different RF frequency, phase and amplitude and different +/-DC applied to the rods or adjacent quadrupole 1103 and 1104 during operation. Electrostatic lens also serves to minimize any capacitive coupling of RF or resonant waveform potentials between quadrupole assemblies 1103 and 1104. Alternatively, single electrostatic lens 1105 can be configured as a plurality of electrostatic lenses to enable focusing or multiple stepped acceleration of ions transferred between quadrupole ion guides 1103 and 1104. Whether or not multipole ion guide 1104 has a different geometric cross section compared to the cross section dimensions of multiple quadrupole assembly 1108, quadrupole 1104 can be operated with a different RF frequency than that applied to quadrupole ion guide 1103. Full triple quadrupole MS and MS/MS function analysis can be achieved with the embodiment of the invention diagrammed in Figure 15 using techniques and methods described previously.

An alternative embodiment of the invention is diagrammed in Figure 16 in which multiple quadrupole ion guide 1208 is configured in higher vacuum pressure stage 1210 and extends into the rod volume described by separate multipole ion guide 1204. Quadrupole ion guide assembly 1203 extends into exit lens 1205 through which ions can be efficiently transferred, even at low kinetic energies, into multipole ion guide 1204. Full triple quadrupole MS and MS/MS functions can be achieved by operating segments 1201, 1202, and quadrupole 1203 and quadrupole 1204 in scanning and static ion  $m/z$  selection and ion CID fragmentation modes as described in the above sections.

An alternative embodiment of the invention is shown in Figure 17 in which an additional multipole ion guide collision cell 1312 has been added to a three vacuum pumping stage multiple quadrupole ion guide mass analyzer. Dual quadrupole or three segment quadrupole ion guide assembly 1308 is configured in higher vacuum pressure vacuum stage 1314 extending into lower pressure vacuum stage 1315. Mass to charge selected and/or fragment ions are transferred from quadrupole ion guide 1309 into multipole ion guide 1310 which is configured in collision region 1312 surrounded by gas partition 1313. Multipole ion guide 1304 serves as the final quadrupole mass analyzer before ions are detected with detector 1305. Analogous to the added multipole ion guide diagrammed in the hybrid API quadrupole TOF hybrid embodiments shown in Figures 10 or 11, collision or reactive gas can be introduced into region 1312 that has a different composition than the background gas composition in vacuum stage 1314. Multipole ion guide 1310 positioned in independent collision region 1312 allows increased experimental flexibility in  $MS/MS^n$  analysis.

Continuous beam  $MS/MS^3$  experiments can be achieved with the embodiment shown in Figure 17 operating with mass to ion charge selection in segment 1301, quadrupole ion guide 1309 and 1304 and DC acceleration or resonant frequency excitation CID ion

fragmentation in segment 1302 and multipole ion guide 1310. When MS only functions are required for a given mass analyzer operation, a simpler embodiment of the invention can be configured to reduce instrument cost, size and complexity.

In one aspect of the invention at least a portion of a segmented or non segmented quadrupole ion guide is configured in a higher pressure vacuum stage where multiple collisions with ions and background neutral gas molecules occur. Figure 18 shows a high pressure non-segmented quadrupole multipole ion guide or mass analyzer 1400 that extends continuously from second vacuum pumping stage 1401 where the background pressure is maintained greater than  $1 \times 10^{-4}$  torr into third vacuum stage 1402 where detector 1403 is located. The quadrupole ion guide assembly 1400 diagrammed in Figure 18 comprises four parallel poles or rods equally spaced around common centerline 1404. In an ideal quadrupole mass analyzer each rod cross section would have a hyperbolic shape but commonly, for ease of manufacture, round rods are used. A cross section of a quadrupole with round rods 104, 105, 106, and 107 is diagrammed in Figure 13. The same RF and +/- DC potentials are applied to opposite rods 104, 106 and 105, 107 respectively for most quadrupole operating modes. Adjacent rods have the same RF and DC amplitude but opposite polarity. In addition, a common DC offset can be applied to all rods 104, 105, 106, and 107. Multiple frequency resonant waveforms may be applied as a dipole to opposite rods or a more complex resonant waveform may be inductively or capacitively added to all four rods.

In the embodiment of the invention diagrammed in Figure 18, non-segmented quadrupole ion guide 1400 analyzer begins in pumping stage two 1401 where the pressure is maintained sufficiently high where ions traversing the length of multipole ion guide 1400 will encounter collisions with neutral background gas molecules. Quadrupole ion guide 1400 can be operated to conduct ion mass to charge selection by applying RF, +/- DC or resonant frequency excitation ion ejection waveforms with or without RF amplitude modulation as describe above. Ion mass to charge selection scanning can be performed by conventional RF and +/- DC voltage amplitude scanning or by stepping RF, +/- DC and resonant frequency waveform notch frequencies over the appropriate ranges to mass analyzer a desired mass to charge range or by a combination of these methods. In  $m/z$  analysis or  $m/z$  selection operating mode, ion collisions with the background gas slow down the selected ion  $m/z$  trajectories in the radial and axial directions as the ions traverse quadrupole ion guide 1400 length in single pass or ion trapping and release mode. Ions spending increased time in quadrupole ion guide 1400 are exposed to an increased number of RF cycles. In this manner higher  $m/z$  selection resolution can be achieved for shorter multipole ion guide lengths than can be attained using a quadrupole mass analyzer with the more conventional method of operating in low background pressure. Operating multipole ion guides in analytical mode with higher pressure background gas in the API MS analyzer diagrammed in Figure 18 allows the configuration of smaller more compact mass analyzer instruments systems with reduced vacuum pumping speed requirements. A smaller quadrupole ion guide size reduces the cost of driver electronics and the higher pressure operation reduces the vacuum system costs. Such a system can achieve improvement in the API MS system performance when compared to an instrument which includes a quadrupole mass analyzer operating at background pressure maintained sufficiently to avoid or minimize ion collisions with neutral background gas.

Atmospheric Pressure Chemical Ionization (APCI) source 1405 can be configured and operated with solvent delivered to APCI nebulizer 1417 tip 1406 at flow rates ranging from

below 500 nl/min to above 2 ml/min. The API MS embodiment diagrammed in Figure 18 can be reconfigured with any of the following alternative sources but is not limited to Electrospray, Inductively Coupled Plasma, Glow Discharge sources, multiple probes mounted one API source, or combinations of different probes configured one API source. Sample bearing solution can be introduced into APCI source 1405 with pressure or positive displacement liquid delivery systems. Liquid delivery systems may include but are not limited to, liquid pumps with or without auto injectors, separation systems such as liquid chromatography or capillary electrophoresis, syringe pumps, pressure vessels, gravity feed vessels or solution reservoirs. APCI source 1405 is operated by applying potentials to cylindrical electrode 1407 and corona needle 1408, endplate electrode 1409 and capillary entrance electrode 1410. Counter current drying gas 1411 is directed to flow through heater 1412 and into APCI source chamber 1405 through endplate nosepiece 1413 opening 1414. The orifice into vacuum as diagrammed in Figure 18 is a dielectric capillary tube 1415 with entrance orifice 1416. The potential of an ion being swept through dielectric capillary tube 1415 into vacuum is described in U.S. patent number 4,542,293. To produce positive ions, negative kilovolt potentials are applied to endplate electrode 1409 with attached electrode nosepiece 1413 and capillary entrance electrode 1410 and positive kilovolt potentials are applied to cylindrical electrode 1407 and corona needle 1408. APCI nebulizer 1417 and APCI heater 1418 remain at ground potential during operation. To produce negative ions, the polarity of the electrodes listed above are reversed. Alternatively, if a nozzle or conductive (metal) capillaries are used as orifices into vacuum, kilovolt potentials can be applied to APCI corona needle 1408 and cylindrical electrode 1407 during operation. Heated capillaries can be configured as the orifice into vacuum operated with or without counter current drying gas.

Unlike an ES source, an APCI source creates sample and solvent molecule vapor prior to ionization. The APCI ionization process, unlike Electrospray, requires gas phase molecule-ion charge exchange reactions. Sample solution is introduced through connecting tube 1420 into APCI probe 1417 and is sprayed with pneumatic nebulization from APCI inlet probe tip 1406. The sprayed liquid droplets traverse cavity 1421 and flow into APCI vaporizer 1418. In the embodiment shown, cavity 1421 is configured with a droplet separator ball. Separator ball 1424 removes larger droplets from the sprays produced by the nebulizer inlet probes to prevent them from entering vaporizer 1418. Separator ball 1424 can be removed when lower solution flow rates are introduced to improve sensitivity. The liquid droplets are evaporated in vaporizer 1418 forming a vapor prior to entering corona discharge region 1422 around and/or downstream of corona discharge needle tip 1423. Additional makeup gas flow may be added independently or through APCI inlet probe assembly to aid in transporting the droplets and resulting vapor through the APCI source assembly. An electric field is formed in APCI source 1405 by applying electrical potentials to cylindrical lens 1407, corona discharge needle 1408, endplate 1409 with nosepiece 1413 and capillary entrance electrode 1410. The applied electrical potentials, counter current gas flow 1411, and the total gas flow through vaporizer 1418 are set to establish a stable corona discharge in region 1422 around and/or downstream of corona needle tip 1423. The ions produced in corona discharge region 1422 by atmospheric pressure chemical ionization are driven by the electric field against counter current bath gas 1411 towards capillary orifice 1416. Ions are swept into vacuum through capillary orifice 1416 and pass through capillary 1415 and into the first vacuum stage 1425. If a capillary is configured with a heater 1426 as an orifice into vacuum with or without counter current drying gas, additional energy can be transferred to the gas and ions in the capillary. This additional energy may be useful for additional drying or to elevate ion internal



energy to aid in ion fragmentation. A portion of the ions entering first stage vacuum 1425 are directed through the skimmer 1427 and into the second vacuum stage 1401.

Ions are produced at or near atmospheric pressure from sample bearing liquid in atmospheric pressure ion source 1405. The ions are delivered into vacuum through dielectric capillary tube 1415 through vacuum partition 1428 carried along by the neutral background gas. The neutral background gas forms a supersonic jet as it expands into vacuum from exit orifice 1429 and accelerates the entrained ions through multiple collisions during the expansion. A portion of the free jet expansion passes through a skimmer 1427 which is part of the vacuum partition 1431 and into second vacuum stage 1401 where background pressures can range from  $10^{-4}$  to  $10^{-1}$  torr depending on the skimmer orifice 1432 size and the pumping speed employed in vacuum stage two 1401 through pump port 1433. Vacuum systems incorporating one or more vacuum pumping stages have been configured to remove background neutral gas as the ions of interest traverse from the API source orifice to the mass analyzer entrance. The cost and size of an API/MS instrument can be reduced if a minimum number of multiple vacuum pumping stages are configured and the pumping speed required for each stage is minimized. Typically, three to four vacuum pumping stages are employed in the lower cost or benchtop API/MS instruments. Ions are delivered to third vacuum pumping stage 1402 through quadrupole ion guide 1400 which pass through vacuum partition 1434. Vacuum stage 1402 evacuated through pumping port 1435. Ions exiting quadrupole ion guide 1400 pass through exit lens 1436 which focuses the ions into the region between lens 1437 and detector 1403. Lens 1437 can be operated as a conversion dynode or a repeller plate either attracting ions or repelling them into detector 1403. Quadrupole ion guide can be operated in single pass or ion trap and release mode during ion mass to charge scanning mode or single or multiple selected ion monitoring operating modes. Selected mass to charge value ion fragmentation operation can be conducted using resonant frequency waveform excitation CID methods as described above.

An alternative embodiment of the invention is diagrammed in Figure 19. Segmented or multiple quadrupole ion guide assembly 1500 is configured in a three stage vacuum system with vacuum stages 1514, 1501 and 1502. Three segment quadrupole ion guide assembly 1500 extends continuously from higher background pressure second vacuum pumping stage 1501 into lower background pressure vacuum stage 1502. With the appropriate individual or shared RF, +/-DC or resonant frequency excitation waveform power supplies applying potentials to the rods of segments or independent quadrupoles 1503, 1504 and 1505, a range of MS or MS/MS functions can be conducted using multiple quadrupole assembly 1500. Continuous ion beam MS/MS experiments can be conducted using the following operating conditions;

1. Quadrupole 1503 is operated in single value or scanning ion mass to charge selection mode, depending on the analytical application, using methods described above.
2. Quadrupole 1504 is operated in RF only mode. Mass to charge selected parent ions are DC accelerated from quadrupole 1503 into quadrupole 1504. The appropriate relative DC offset potentials are applied to the rods of quadrupoles 1503 and 1504 so that ions are accelerated across junction 1507 with sufficient velocity to cause DC acceleration CID ion fragmentation. Alternatively or in combination, resonant excitation frequencies can be applied to the rods of

- quadrupole 1504 to cause CID ion fragmentation of parent and/or fragment ions in quadrupole 1504.
3. Fragment ions are transferred across junction 1508 into quadrupole 1505 without fragmentation.
  4. Quadrupole 1505 is operated in single value mass to charge scanning mass to charge selection mode, depending on the analytical application. The ion mass to charge selection scanning ramps of quadrupoles 1503 and 1505 can be synchronized to perform neutral loss scans or monitoring of selected fragmentation events.
  5. Ions passing from quadrupole ion guide 1505 through lens 1517 are accelerated into conversion dynode 1518. The resulting secondary electrons and photons are detected with electron or photomultiplier 1519. Alternatively, ions can be accelerated directly into electron multiplier 1519 and detected.

Electrostatic lenses can be added in junction 1507 isolating quadrupole ion guides 1503 and 1504 and in junction 1508 isolating quadrupole ion guides 1504 and 1505. Said electrostatic lenses would serve to decouple any rapidly changing RF and +/- DC potentials applied to the rods of quadrupoles 1503 and 1505 during mass to charge scanning from effecting the potentials applied to the rods of quadrupole assembly 1504. The added electrostatic isolations lenses would also reduce any fringing field effects for ions traversing junctions 1507 and/or 1508 allowing different RF frequency, phase and amplitude potentials to be applied to the rods of quadrupoles 1503, 1504 and 1505 of multiple quadrupole assembly 1500. The triple quadrupole mass analyzer as diagrammed in Figure 19 is configured with a medium pressure glow discharge ion source comprising electrodes 1511 and 1512, sample gas inlet 1510 and pumping port 1514. A portion of the ions produced in the glow discharge source pass through skimmer 1513 and into multiple quadrupole mass analyzer assembly 1500. Alternatively, triple quadrupole 1500 as diagrammed in Figure 19 can be configured with Electrospray and APCI atmospheric pressure ion sources with the glow discharge source vacuum stage serving as the first vacuum stage of a three vacuum stage instrument.

Multiple quadrupole ion guide assembly 1500 is reconfigured in a single vacuum pumping stage in an alternative embodiment of the invention as diagrammed in Figure 21. Individual quadrupole assemblies 1715, 1717 and 1719 are configured along a common centerline in higher background pressure vacuum pumping stage 1702. The triple quadrupole mass analyzer embodiment as diagrammed in Figure 21 is configured in a three vacuum pumping stage system with vacuum stages 1701, 1702 and 1703 evacuated through vacuum pumping ports 1711, 1712 and 1713 respectively. Exit lens 1704 configured as part of but electrically insulated from vacuum partition 1705, minimizes the neutral gas conductance into third vacuum stage 1703 wherein conversion dynode and electron multiplier detector 1706 are configured. This allows the maintenance of lower background pressure vacuum in vacuum stage 1703 with smaller, reduced vacuum pumping speed and lower cost vacuum pumps. Ions entering triple quadrupole assembly 1700 through the orifice in skimmer 1709 electrically insulated from vacuum partition 1710 can undergo MS or MS/MS analysis using operating methods as described above for triple quadrupole assembly 1500 diagrammed in Figure 19. Alternatively, as described above for multiple quadrupole assembly 1500, electrostatic lenses can be configured in junctions 1716 and 1718 to isolate quadrupoles 1715 and 1719 from quadrupole 1717. DC voltages can be switched to said added electrostatic lenses configured in junctions 1716 and 1718 to allow independent trapping and release of ions from quadrupoles 1715, 1717 and 1719 for specific analytical applications. Multiple resonant frequency ejection and excitation waveforms can be applied to the rods of

quadrupoles 1715, 1717 and/or 1719 to achieve quasi MS/MS<sup>n</sup> mass analysis, as described in an earlier section. For example, to conduct a quasi MS/MS<sup>3</sup> mass analysis, a first mass spectrum is acquired using MS/MS operating mode with parent ion mass to charge selection conducted in quadrupole 1715. Parent ions are fragmented in quadrupole 1717 using single mass range resonant frequency excitation CID ion fragmentation operation or DC acceleration CID ion fragmentation or a combination of both and mass to charge scanning is conducted with quadrupole 1719. A second mass spectrum is acquired with two mass range resonant frequency excitation CID ion fragmentation conducted in quadrupole 1717 where second generation ions are produced by simultaneously conducting parent and first generation ion CID fragmentation. Alternatively, single mass range resonant frequency excitation CID ion fragmentation of first generation fragment ions combined with DC acceleration CID fragmentation of parent ions is conducted in quadrupole 1717 while acquiring the second mass spectrum by scanning quadrupole 1719. The first acquired mass spectrum is then subtracted from the second acquired mass spectrum to produce a quasi MS/MS<sup>3</sup> mass spectrum of second generation fragment ions.

API MS analyzer cost and complexity can be further reduced by configuring the ion detectors in higher pressure vacuum stages according to the invention. Multichannel plate detectors are available that can operate in pressures higher than  $1 \times 10^{-4}$  torr due to the configuration of thin plates comprising small diameter and short length channels. In said multichannel plate detectors, the cascading electron path resulting from an ion impact in a detector channel is shorter than the background pressure mean free path, minimizing electron scattering and loss of signal. Single segment quadrupole ion guide 1800 is configured in a two vacuum pumping stage Electrospray mass analyzer configured according to the invention as diagrammed in Figure 22. First vacuum stage 1801 is evacuated through pumping port 1811 typically backed by a rotary pump. Second vacuum stage 1802 is evacuated through pumping port 1812 and can be backed by a small turbomolecular pump or even a rotary vacuum pump. Quadrupole ion guide 1800 is configured in higher pressure vacuum stage 1802 with exit lens 1804 and multichannel plate detector 1806. Ions passing through the orifice in skimmer 1809 are mass to charge analyzed in quadrupole 1800 using single value or selected ion monitoring ion mass to charge selection operation or scanning mass to charge selection operation as described above. The embodiment of the invention as diagrammed in Figure 22 can be configured as a small, compact and low cost instrument while retaining full MS analysis capability. MS/MS and even quasi MS/MS<sup>n</sup> mass analysis functions can be performed using the triple quadrupole embodiment of the invention as diagrammed in Figure 23.

Individual quadrupole assemblies 1913, 1915 and 1917 are configured along a common centerline in higher background pressure vacuum stage 1902. The Electrospray MS analyzer as diagrammed in Figure 23 is configured with two vacuum pumping stages 1901 and 1902 evacuated through vacuum ports 1911 and 1912 respectively. Triple quadrupole ion guide assembly 1900, exit lens 1904 and multichannel plate detector 1906 are configured in second vacuum pumping stage 1902. Using methods described for multiple quadrupole ion guides configured as diagrammed in Figures 21 and 19, a range of MS/MS and quasi MS/MS<sup>n</sup> mass analysis functions can be conducted using the embodiment of the invention as diagrammed in Figure 23. Individual quadrupole assemblies 1913, 1915 and 1917 can be operated in single pass or ion trap and release mode by coordinating DC offset potentials applied to adjacent quadrupoles and skimmer 1909 and exit lens 1904. Alternatively electrostatic lenses may be

configured in junctions 1914 and 1917 between quadrupoles 1913 and 1915 and quadrupoles 1915 and 1917 respectively allowing independent ion trapping and release operation independently in individual quadrupoles 1913, 1915 and 1917. The configuration of electrostatic lenses in junctions 1914 and 1916 also allows the operation of all three quadrupoles with different RF frequency, phase and amplitude applied to the rods of each quadrupole during MS and MS/MS analysis. The embodiment of the invention as diagrammed in Figure 23 allows the configuration of a small, compact and low cost API source triple quadrupole mass analyzer. A range of MS, MS/MS and quasi MS/MS<sup>n</sup> mass analysis operations can be conducted using said API source triple quadrupole mass analyzer configured according to the invention.

Although the invention has been described in terms of specific preferred embodiments, it will be obvious and understood to one of ordinary skill in the art that various modifications and substitutions are included within the scope of the inventions as defined in the appended claims. In particular other types of mass analyzers including but not limited to conventional quadrupole, magnetic sector, Fourier Transform three dimensional ion traps and Time of Flight mass analyzers can be configured with embodiments of the invention as described herein. Any type of ion source including but not limited to the atmospheric pressure ion sources described herein and the ion sources that produce ions in vacuum listed in the above description can also be interfaced with embodiments of the invention described herein. In addition, various references relevant to the disclosure of the present application are cited above, and are hereby incorporated herein by reference.

## Claims

We claim:

1. An apparatus for analyzing chemical species, comprising:
  - (a) an ion source for operation at substantially atmospheric pressure to produce ions from a sample substance;
  - (b) a vacuum system with at least one vacuum pumping stage;
  - (c) a detector configured in at least one of said vacuum pumping stages;
  - (d) configuring at least two multipole ion guides in at least one of said vacuum pumping stages wherein at least a portion of each said multipole ion guide is positioned in at least one of said vacuum pumping stages wherein the background pressure in said vacuum stage is maintained sufficiently high so that collisions between said ions and neutral gas molecules occur with ions in said two multipole ion guides; and,
  - (e) means for conducting mass to charge selection in at least one of said multipole ion guides.
2. An apparatus according to claim 1, wherein said ion source is an Electrospray ion source.
3. An apparatus according to claim 1, wherein said ion source is an Atmospheric Pressure Chemical Ionization ion source.
4. An apparatus according to claim 1, wherein said ion source is an Inductively Coupled Plasma ion source.
5. An apparatus according to claim 1, wherein said ion source is an Glow Discharge ion source.
6. An apparatus according to claim 1, wherein said multipole ion guide is a quadrupole.
7. An apparatus according to claim 1, wherein said multipole ion guide is a hexapole.
8. An apparatus according to claim 1, wherein said multipole ion guide is a octapole.
9. An apparatus according to claim 1, wherein said multipole ion guide has more than eight poles.
10. An apparatus for analyzing chemical species, comprising:
  - (a) an ion source for operation at substantially atmospheric pressure to produce ions from a sample substance;
  - (b) a vacuum system with at least one vacuum pumping stage;
  - (c) a detector configured in at least one of said vacuum pumping stages;
  - (d) a mass analyzer for conducting mass to charge analysis;
  - (e) configuring said at least two multipole ion guides in at least one said vacuum pumping stages wherein at least a portion of each of said at least two multipole ion guides is positioned in at least one of said vacuum pumping stages wherein the background pressure in said vacuum stage is maintained sufficiently high so that collisions between said ions and neutral gas molecules occur with ions in said two multipole ion guides;

- (f) means for conducting mass to charge selection in at least one of said multipole ion guides; and,
  - (g) conducting mass to charge analysis in said mass analyzer.
11. An apparatus according to claim 10 wherein said at least two multipole ion guides are configured in series along a common centerline wherein said ions can be transferred from one multipole ion guide to the next.
  12. An apparatus according to claim 10, wherein said mass analyzer is a quadrupole mass spectrometer.
  13. An apparatus according to claim 10, wherein said mass analyzer is a quadrupole mass analyzer.
  14. An apparatus according to claim 10, wherein said at least two multipole ion guides are configured with said mass analyzer to form a triple quadrupole mass analyzer.
  15. An apparatus according to claim 10, wherein said mass analyzer is a magnetic sector mass spectrometer.
  16. An apparatus according to claim 10, wherein said mass analyzer is a Fourier Transform mass spectrometer.
  17. An apparatus according to claim 10, wherein said mass analyzer is a ion trap mass spectrometer.
  18. An apparatus according to claim 10, wherein said mass analyzer is a Time-Of-Flight mass spectrometer.
  19. An apparatus according to claim 10, wherein said mass analyzer is a Time-Of-Flight mass spectrometer configured with orthogonal pulsing.
  20. An apparatus according to claim 10, wherein said mass analyzer is a Time-Of-Flight mass spectrometer configured with linear pulsing.
  21. An apparatus according to claim 10, wherein said mass analyzer is a Time-Of-Flight mass spectrometer comprising an ion reflector.
  22. An apparatus for analyzing chemical species, comprising:
    - (a) an ion source for operation at substantially atmospheric pressure to produce ions from a sample substance;
    - (b) a vacuum system with at least one vacuum pumping stage;
    - (c) a detector configured in at least one of said vacuum pumping stages;
    - (d) configuring said at least two multipole ion guides in at least one said vacuum pumping stage wherein at least a portion of each said multipole ion guide is positioned in at least one of said vacuum pumping stages wherein the background pressure in said vacuum stage is maintained sufficiently high so that collisions between said ions and neutral gas molecules occur with ions in said two multipole ion guides;

- (e) means for conducting mass to charge selection in at least one of said multipole ion guides; and,
  - (f) means for conducting collisional induced dissociation ion fragmentation in at least one said multipole ion guides.
23. An apparatus for analyzing chemical species, comprising:
- (a) an ion source for operation at substantially atmospheric pressure to produce ions from a sample substance;
  - (b) a vacuum system with at least one vacuum pumping stage;
  - (c) a detector configured in at least one of said vacuum pumping stages;
  - (d) a mass analyzer for conducting mass to charge analysis;
  - (e) configuring said at least two multipole ion guides in at least one said vacuum pumping stages wherein at least a portion of each of said at least two multipole ion guides is positioned in at least one of said vacuum pumping stages wherein the background pressure in said vacuum stage is maintained sufficiently high so that collisions between said ions and neutral gas molecules occur with ions in said two multipole ion guides;
  - (f) means for conducting mass to charge selection in at least one of said multipole ion guides;
  - (g) means for conducting collisional induced dissociation ion fragmentation in at least one said multipole ion guides; and,
  - (h) conducting mass to charge analysis in said mass analyzer.
24. A method for analyzing chemical species utilizing an ion source, a vacuum system with at least one vacuum pumping stage, a mass analyzer, at least two multipole ion guides configured in a adjacent alignment along a common centerline in at least one said vacuum stage and a detector, said method comprising:
- (a) producing ions in said ion source;
  - (b) delivering said ions into said at least one said multipole ion guide;
  - (c) operating at least a portion of said at least two multipole ion guides in a background pressure in at least one said vacuum stage wherein collisions occur between said ions and the neutral background molecules for said ions traversing said at least one said multipole ion guide;
  - (d) conducting mass to charge selection of said ions in at least one said multipole ion guide;
  - (e) conducting collisional induced dissociation in at least one said multipole ion guide;
  - (f) transferring said ions from the first said multipole ion guide into the second said multipole ion guide; and,
  - (g) conducting mass analysis of the ion population resulting from said mass to charge selection and said ion fragmentation steps performed in said first and second multipole ion guides.

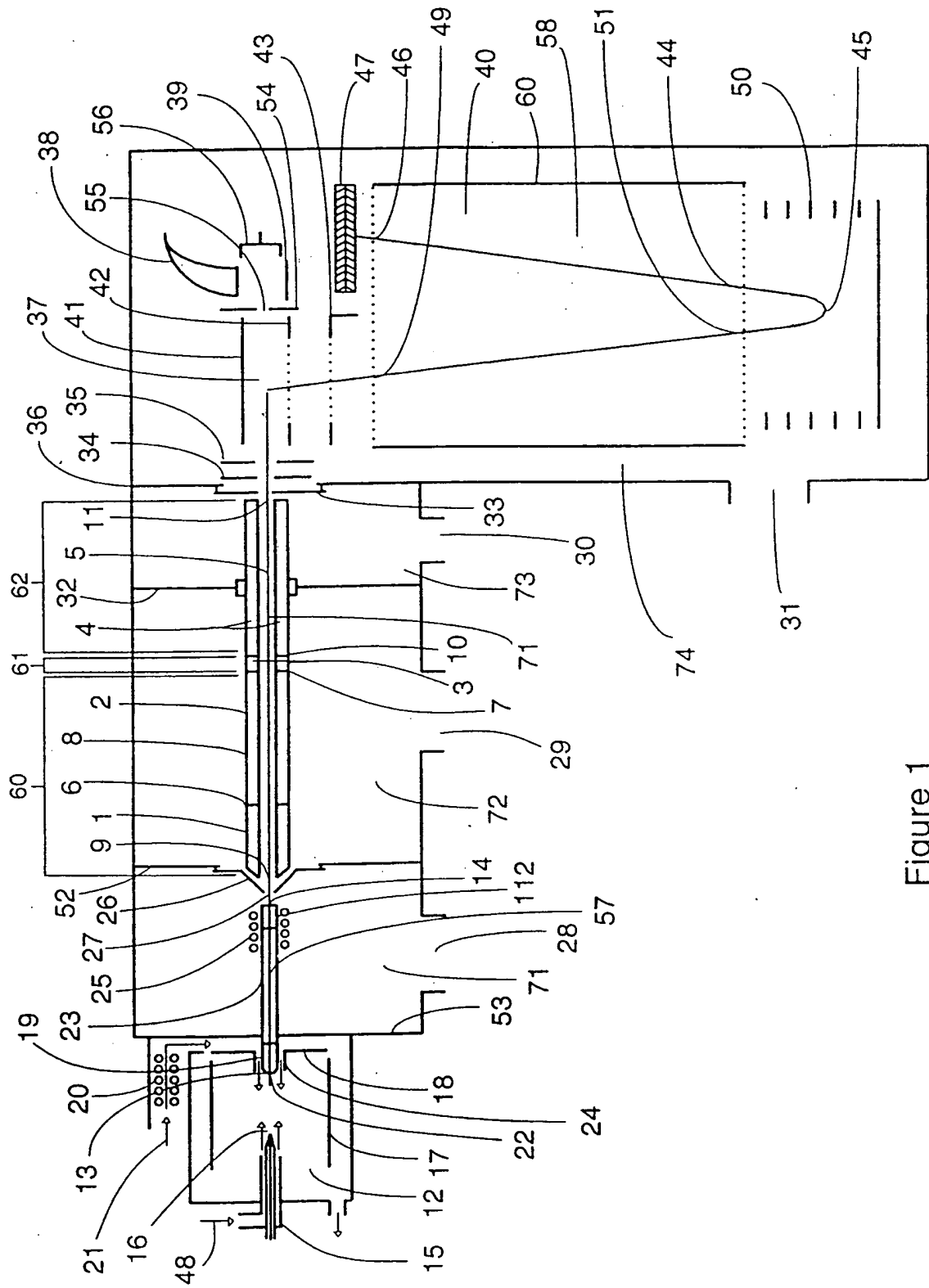


Figure 1



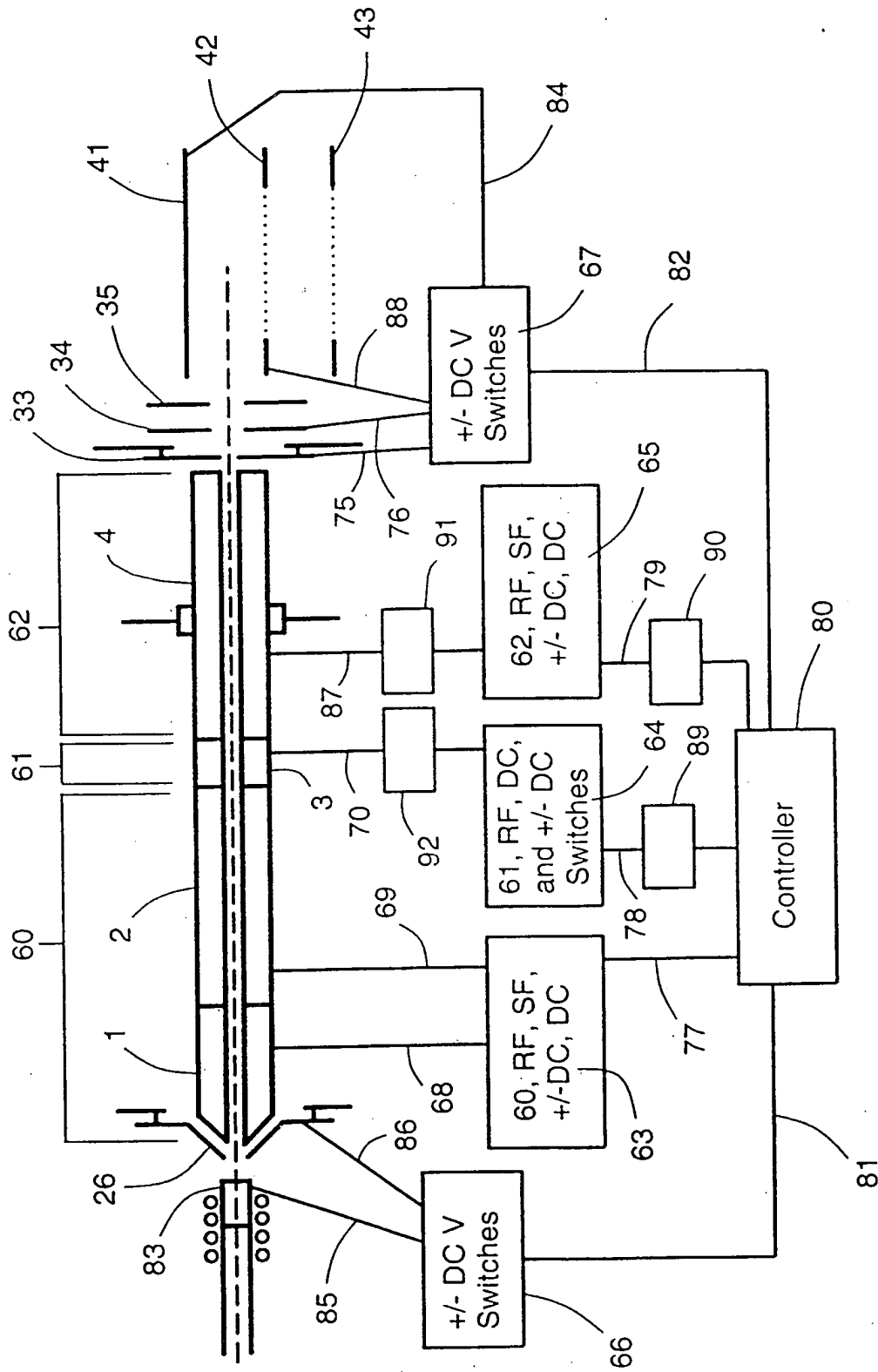


Figure 2

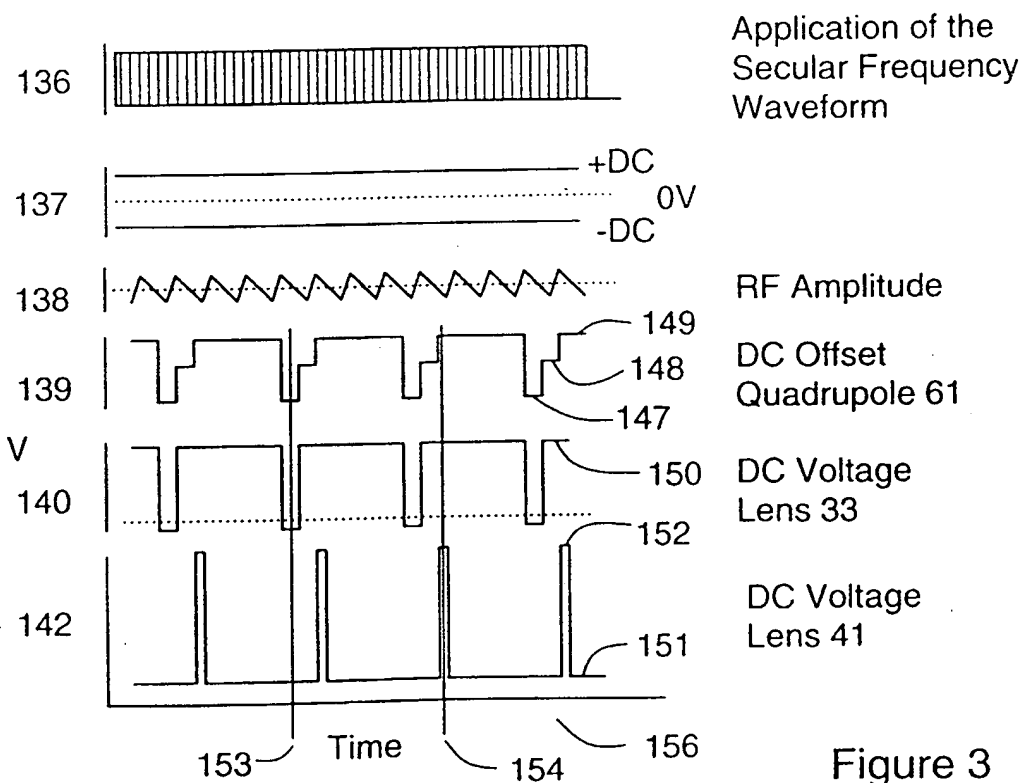
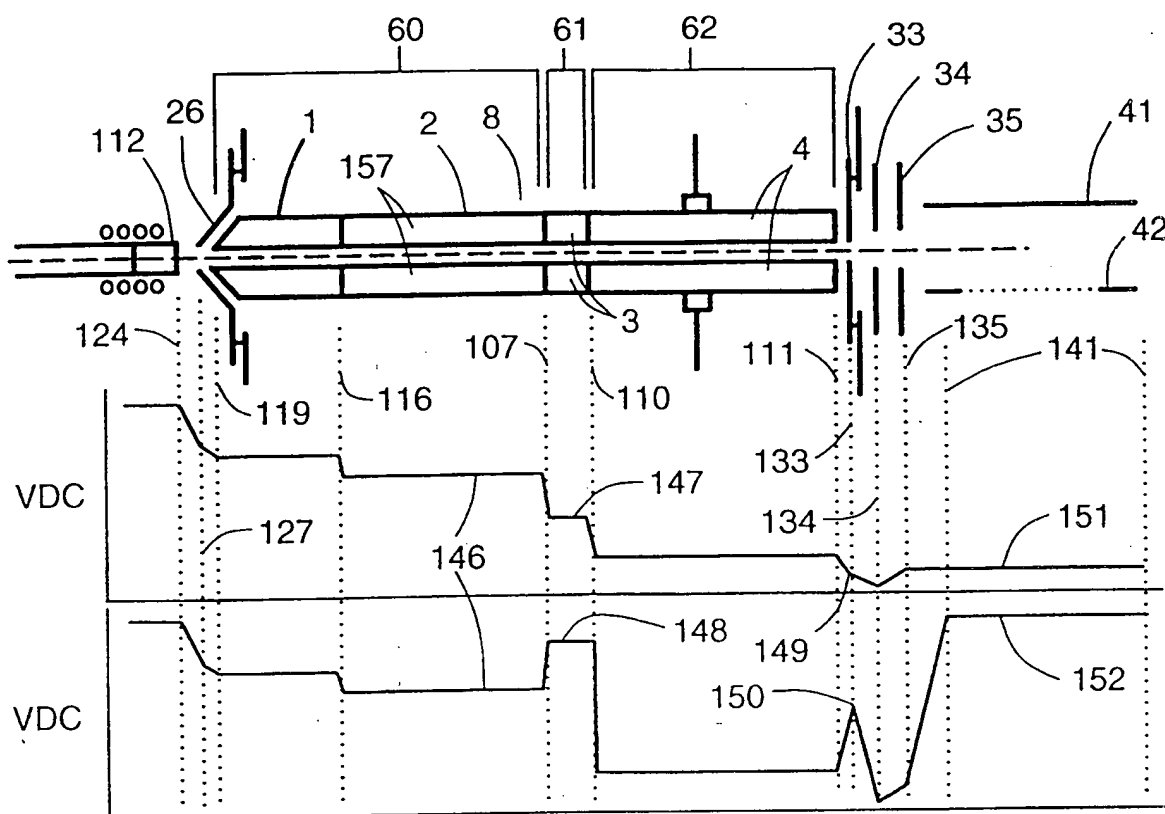


Figure 3

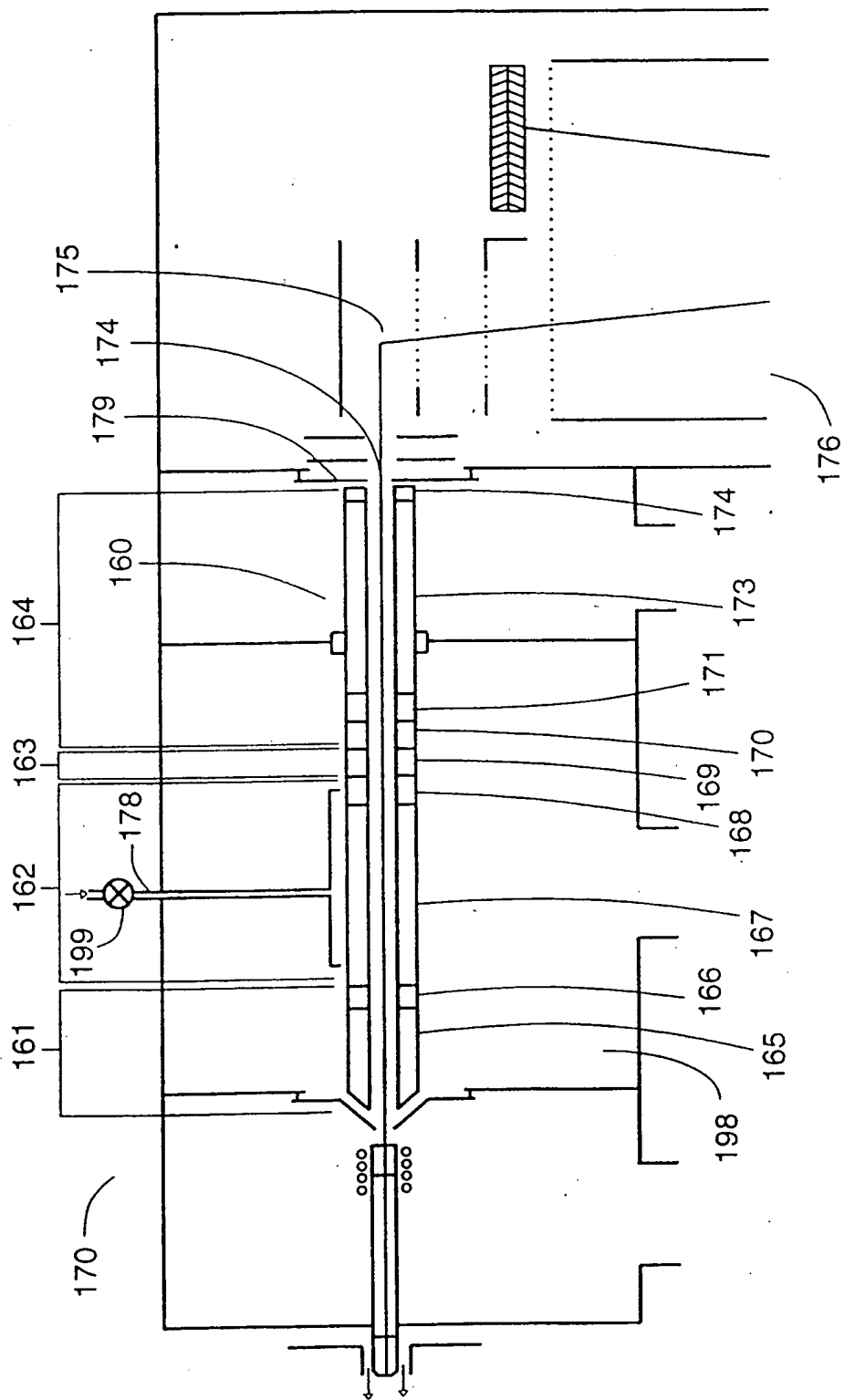


Figure 4

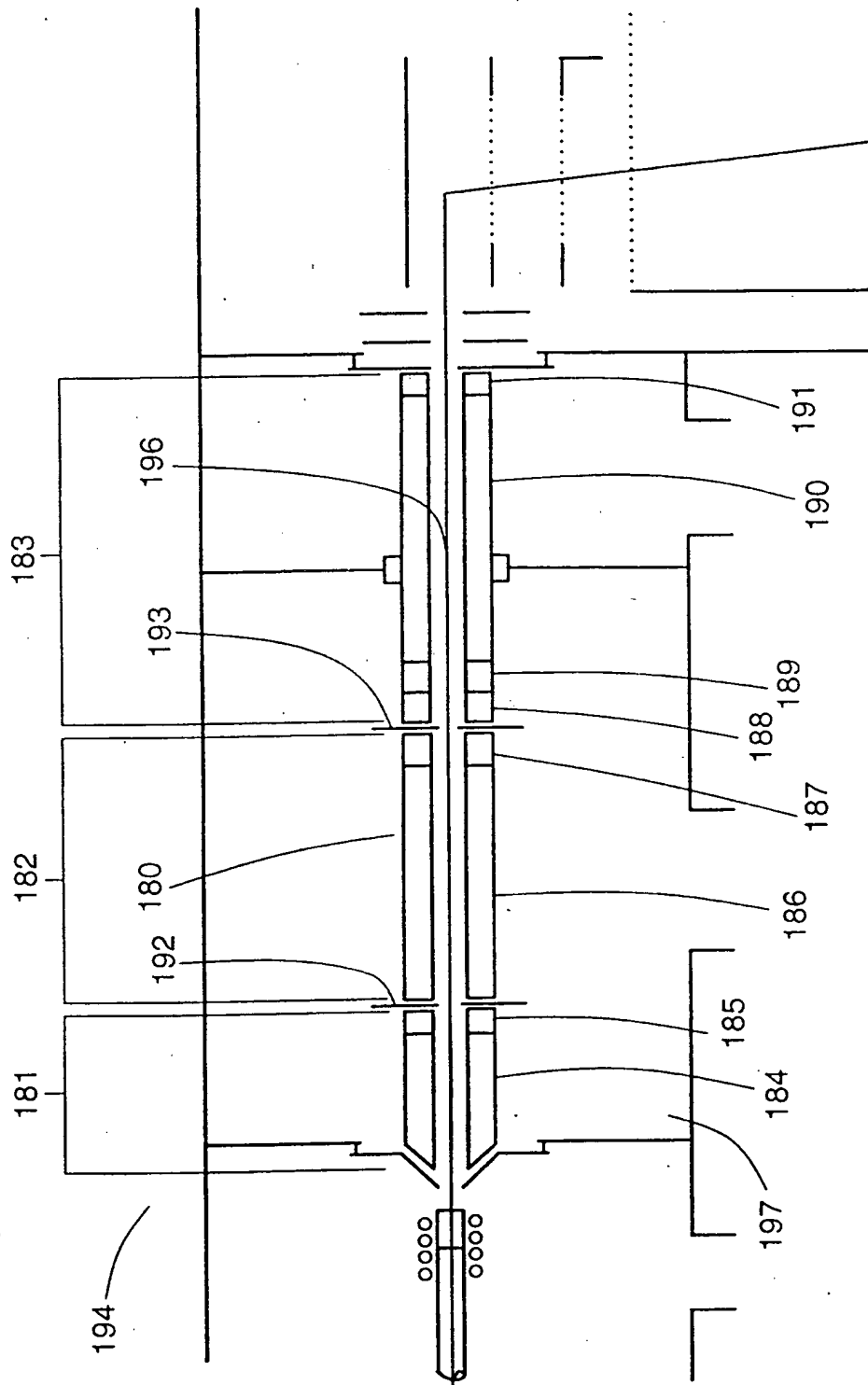


Figure 5

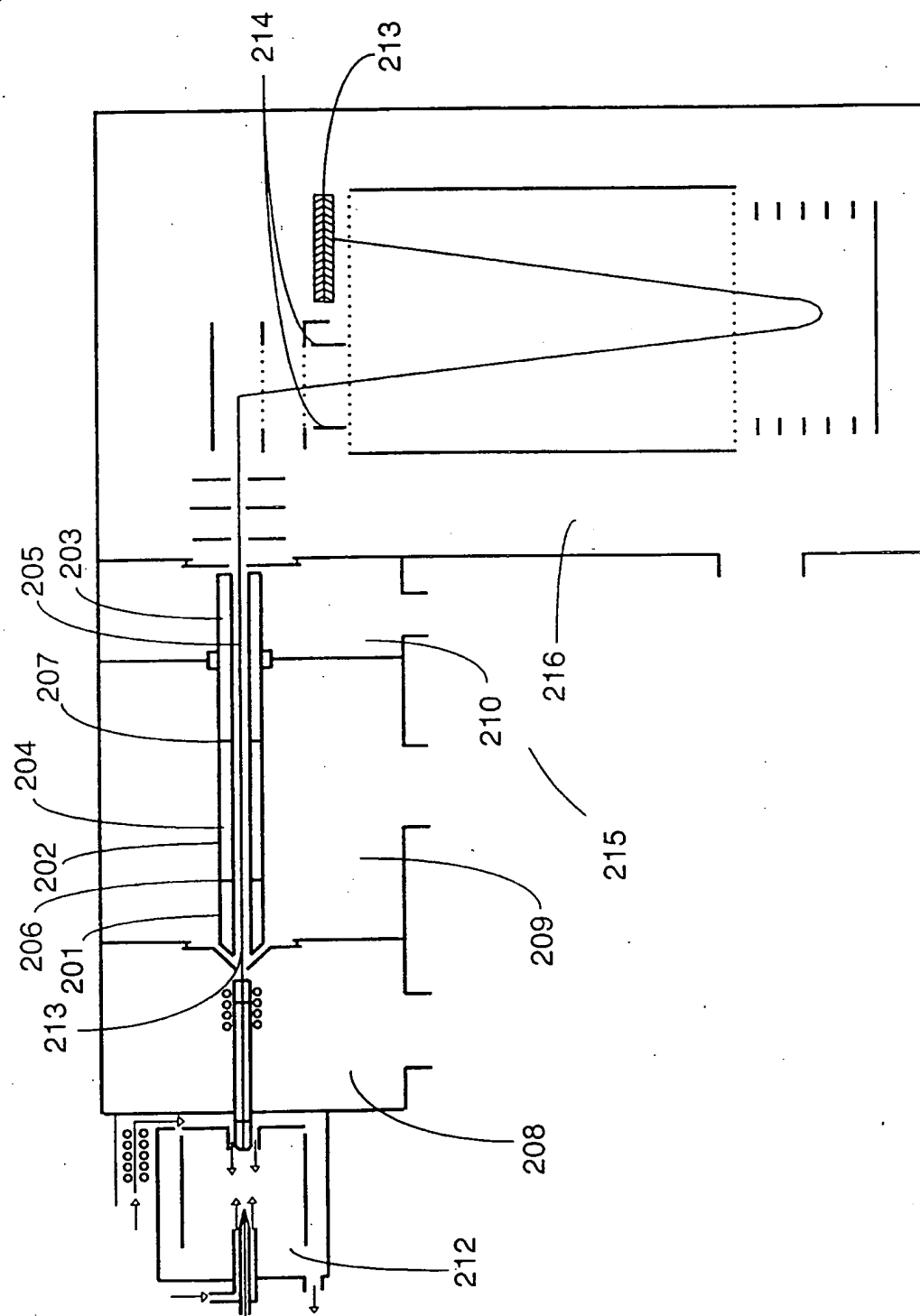


Figure 6

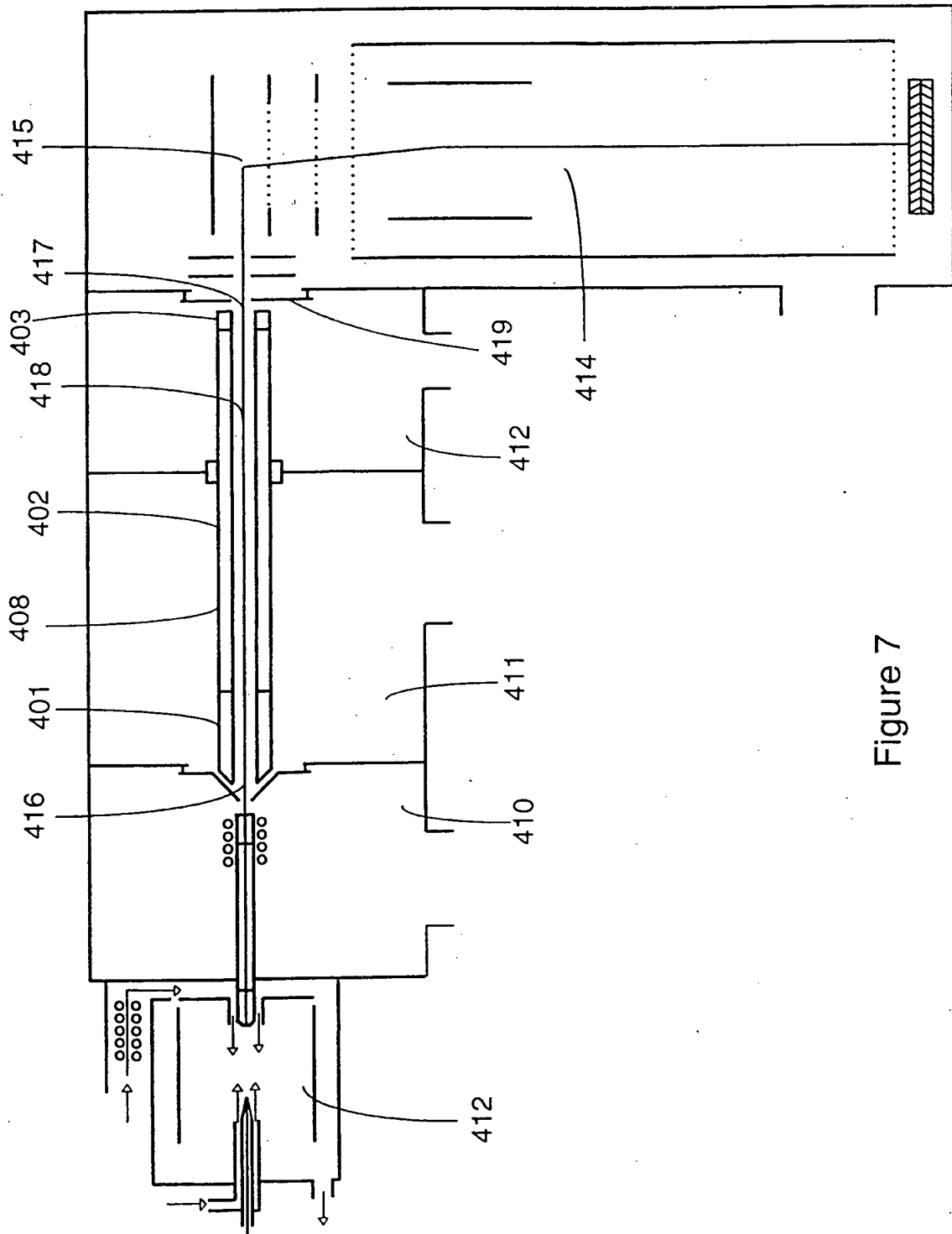


Figure 7

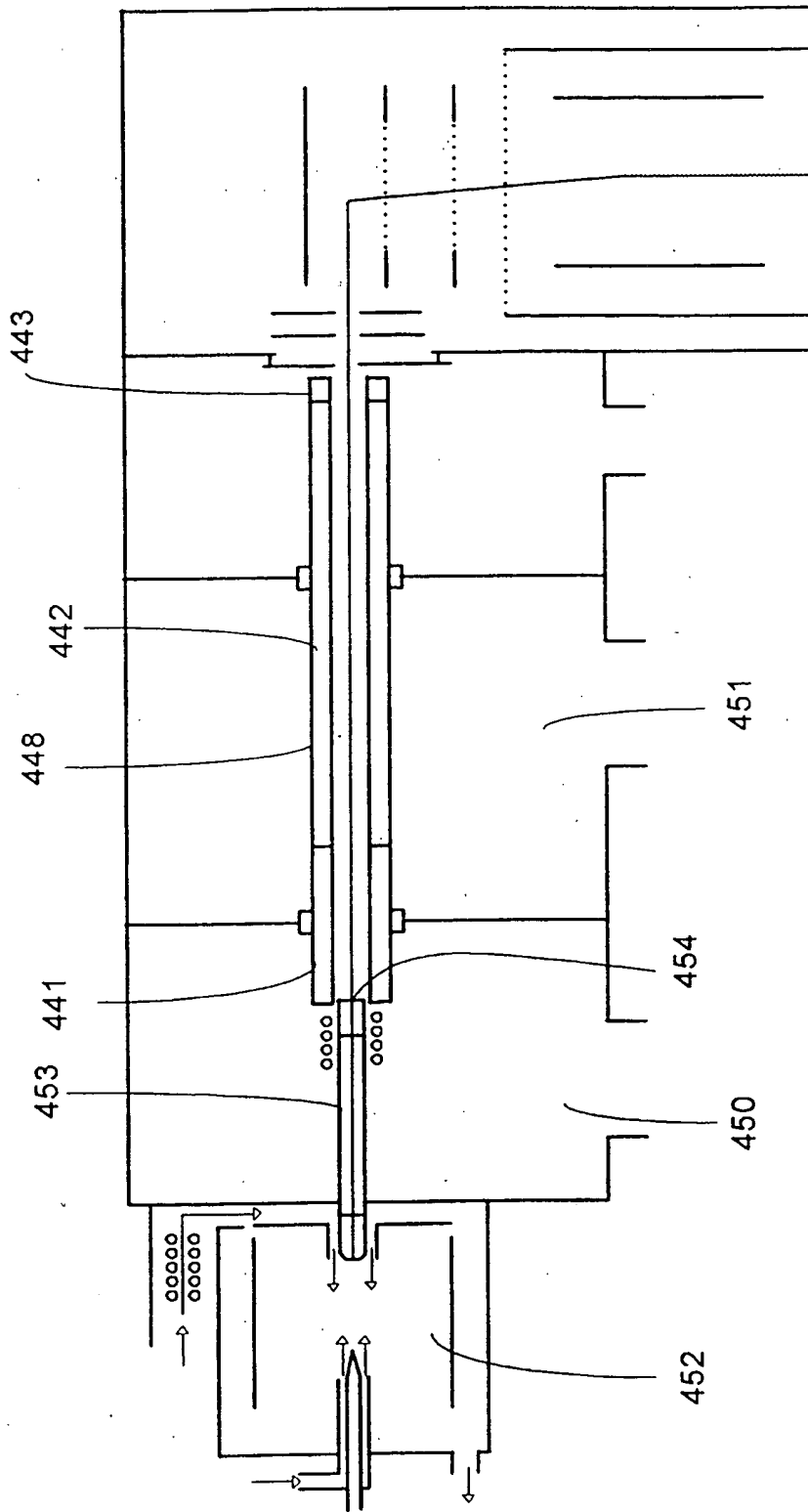


Figure 8

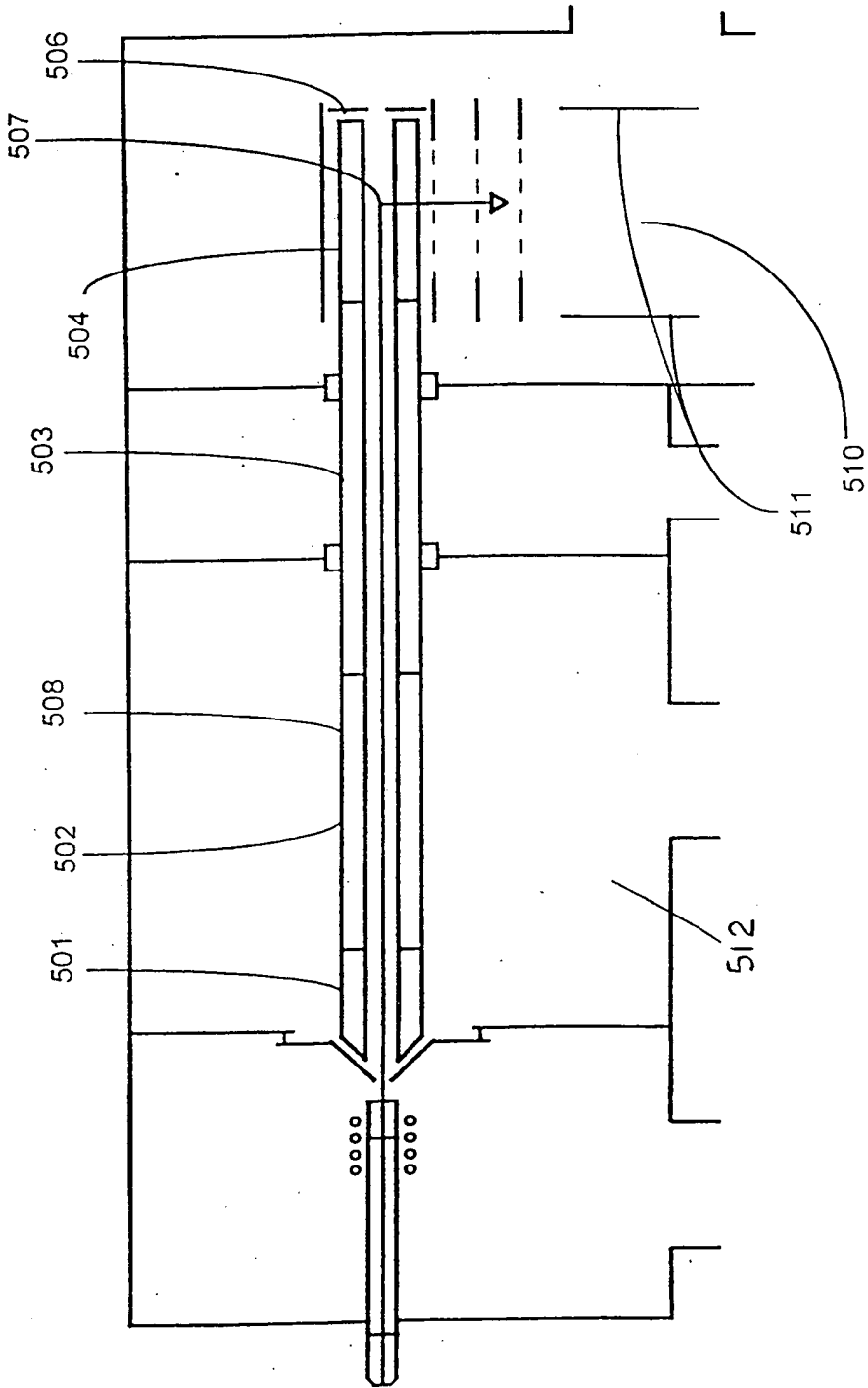


Figure 9



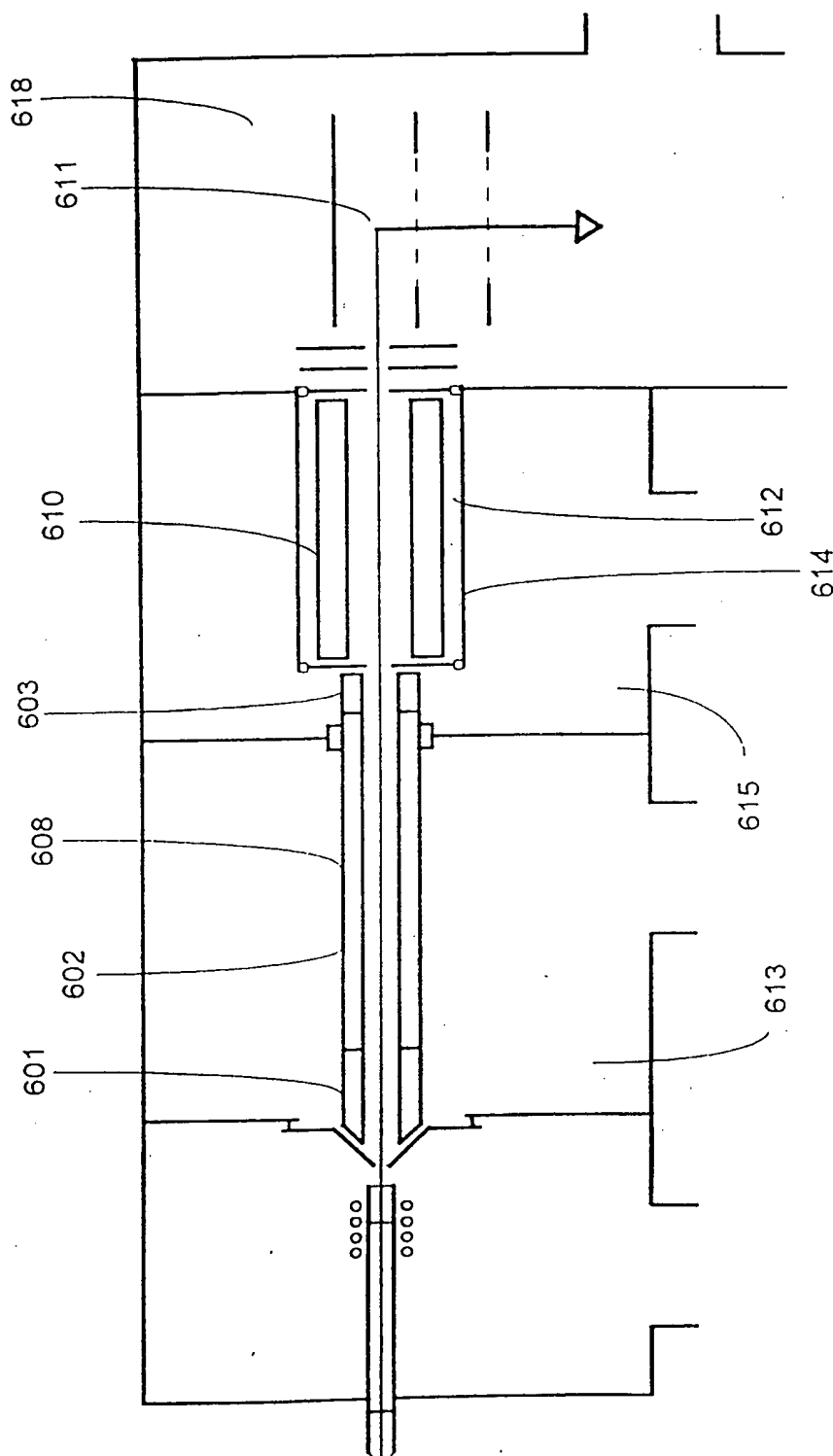


Figure 10

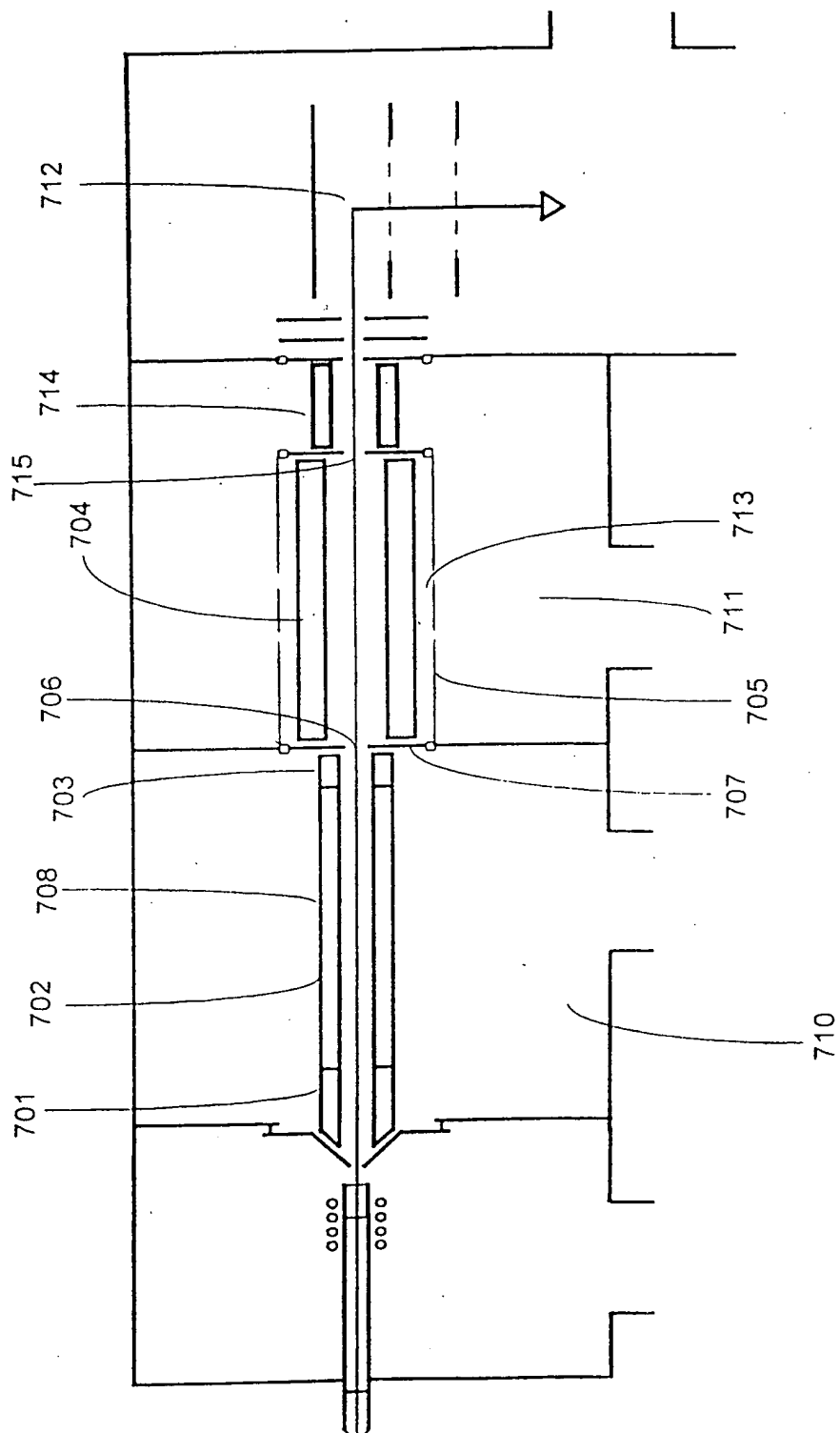


Figure 11

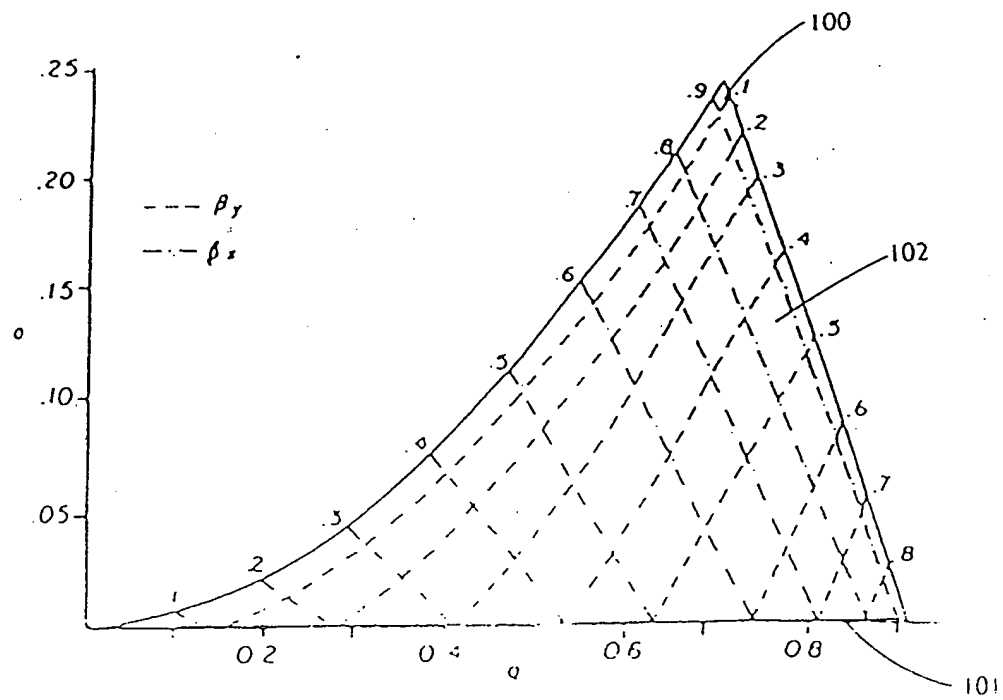


Figure 12

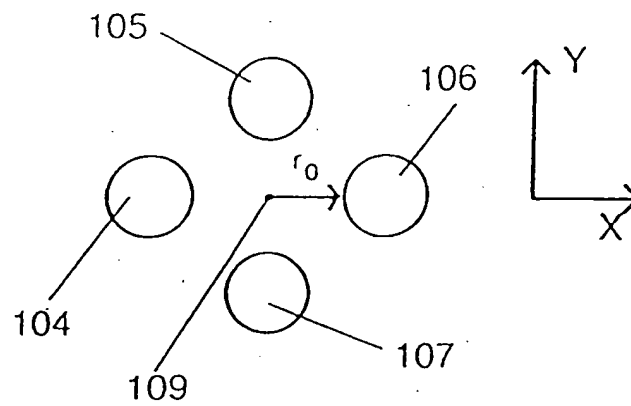


Figure 13

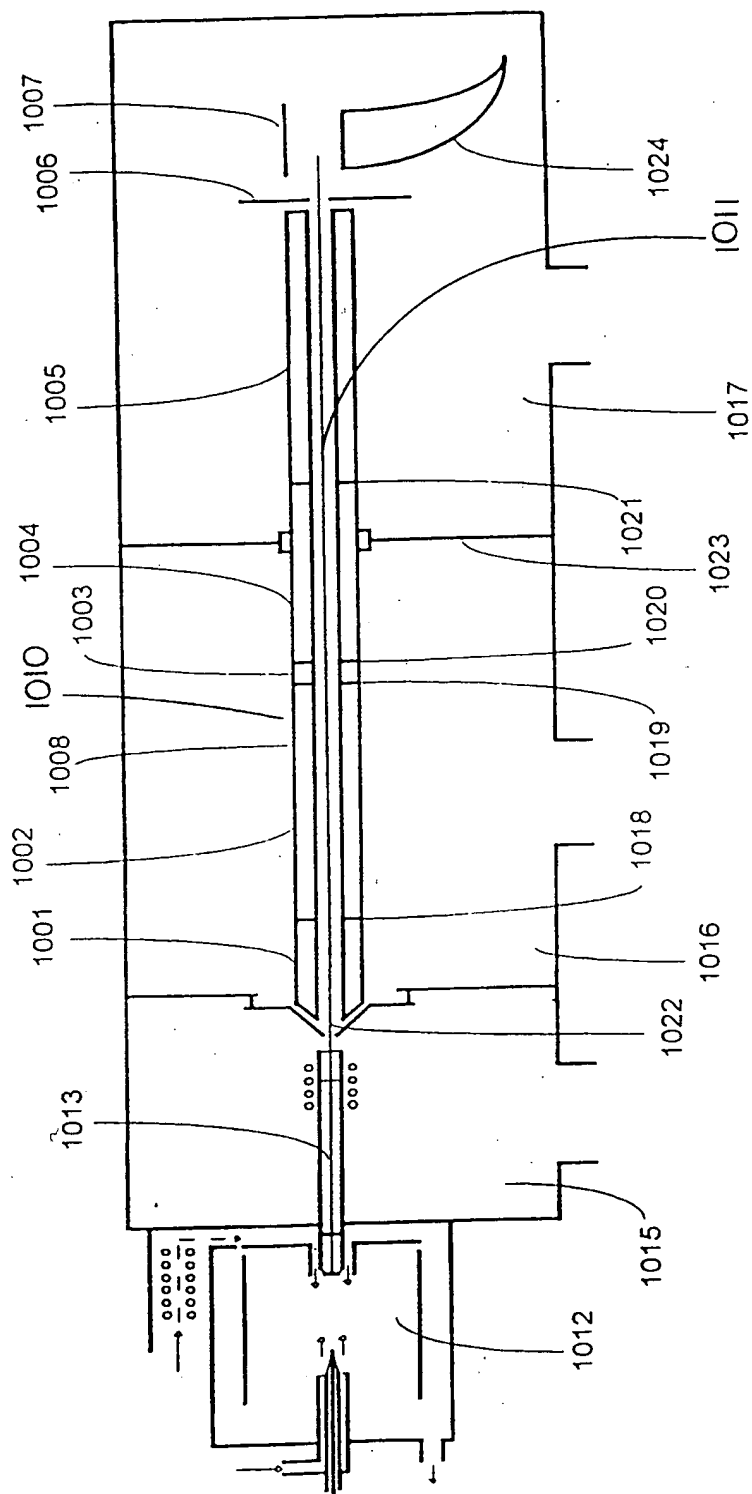


Figure 14

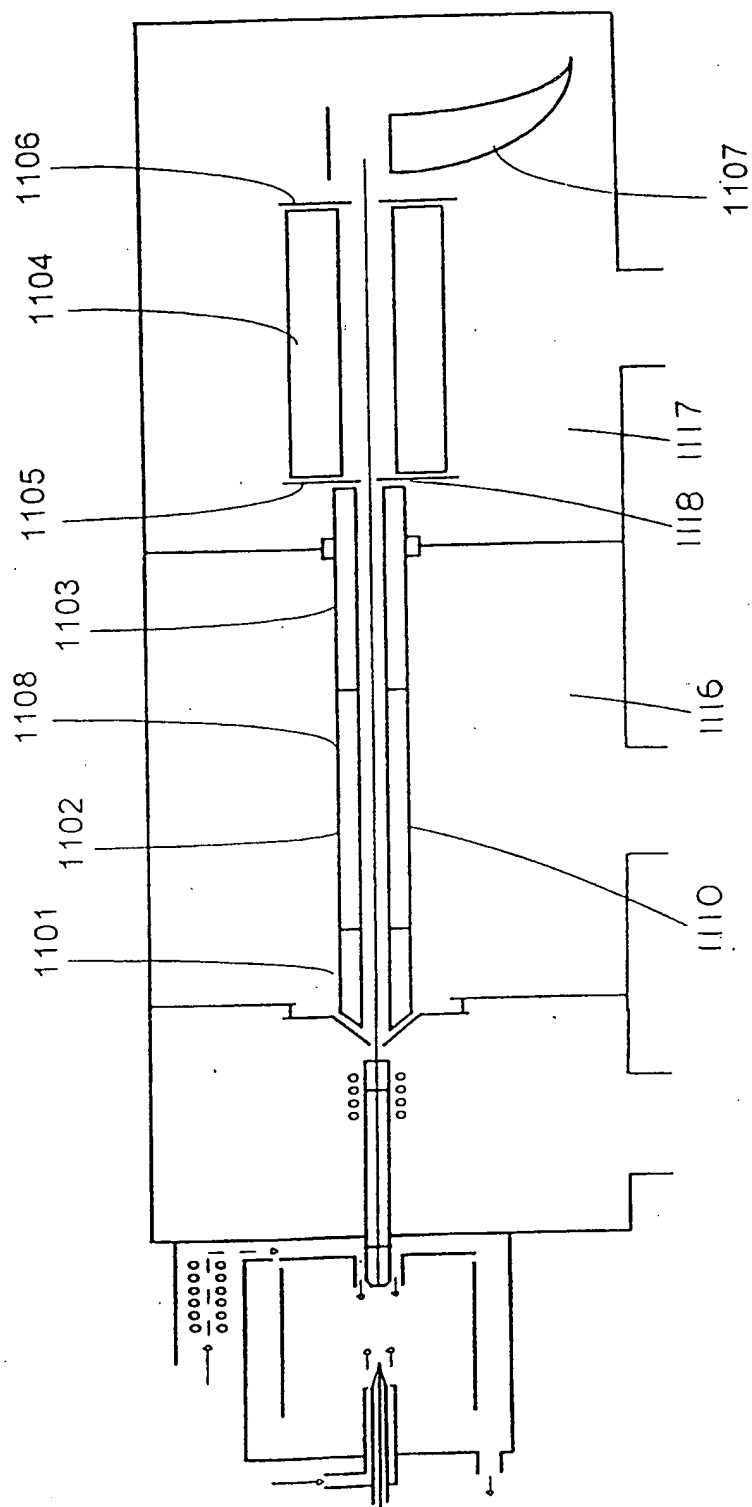


Figure 15

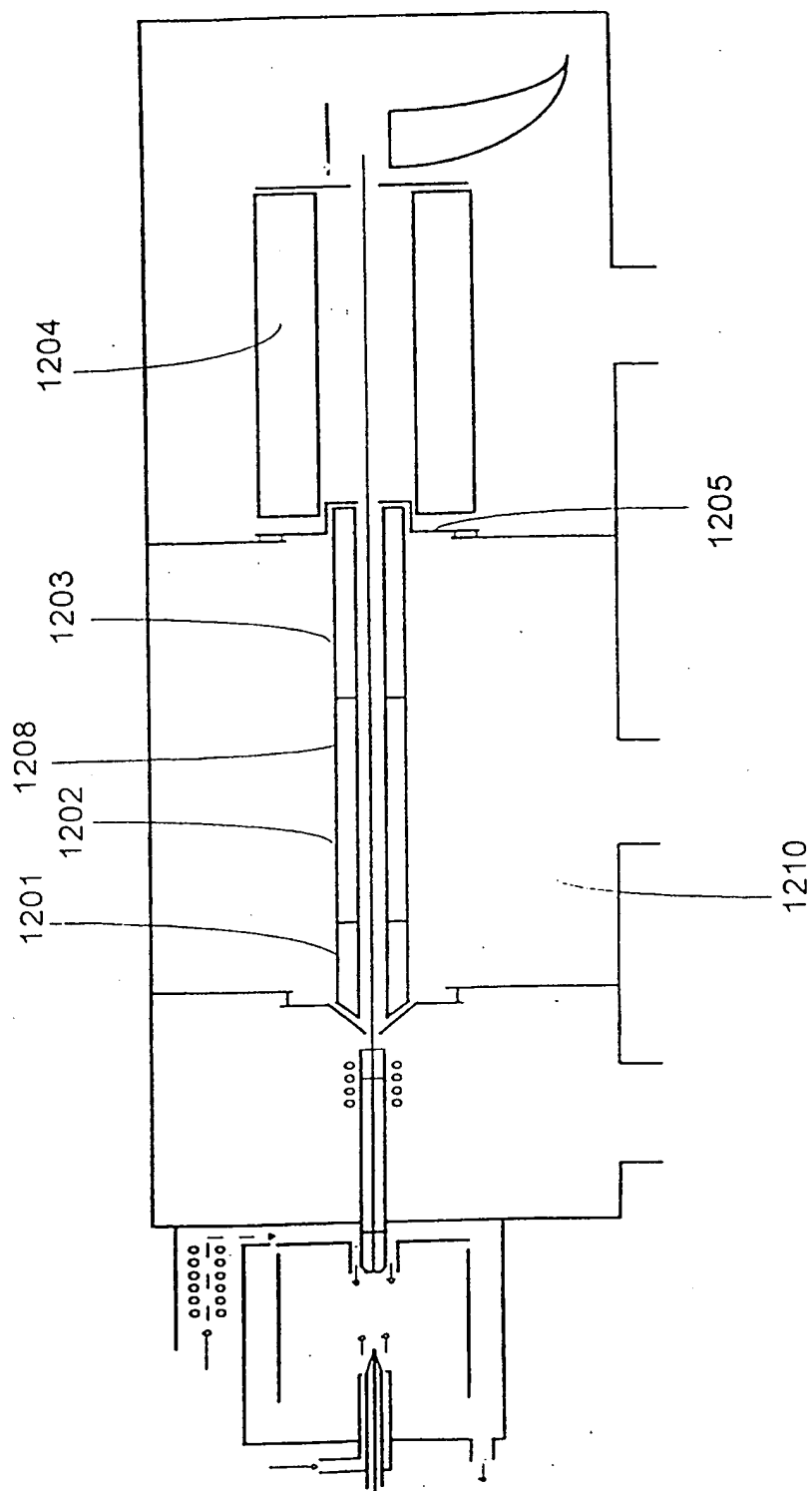


Figure 16

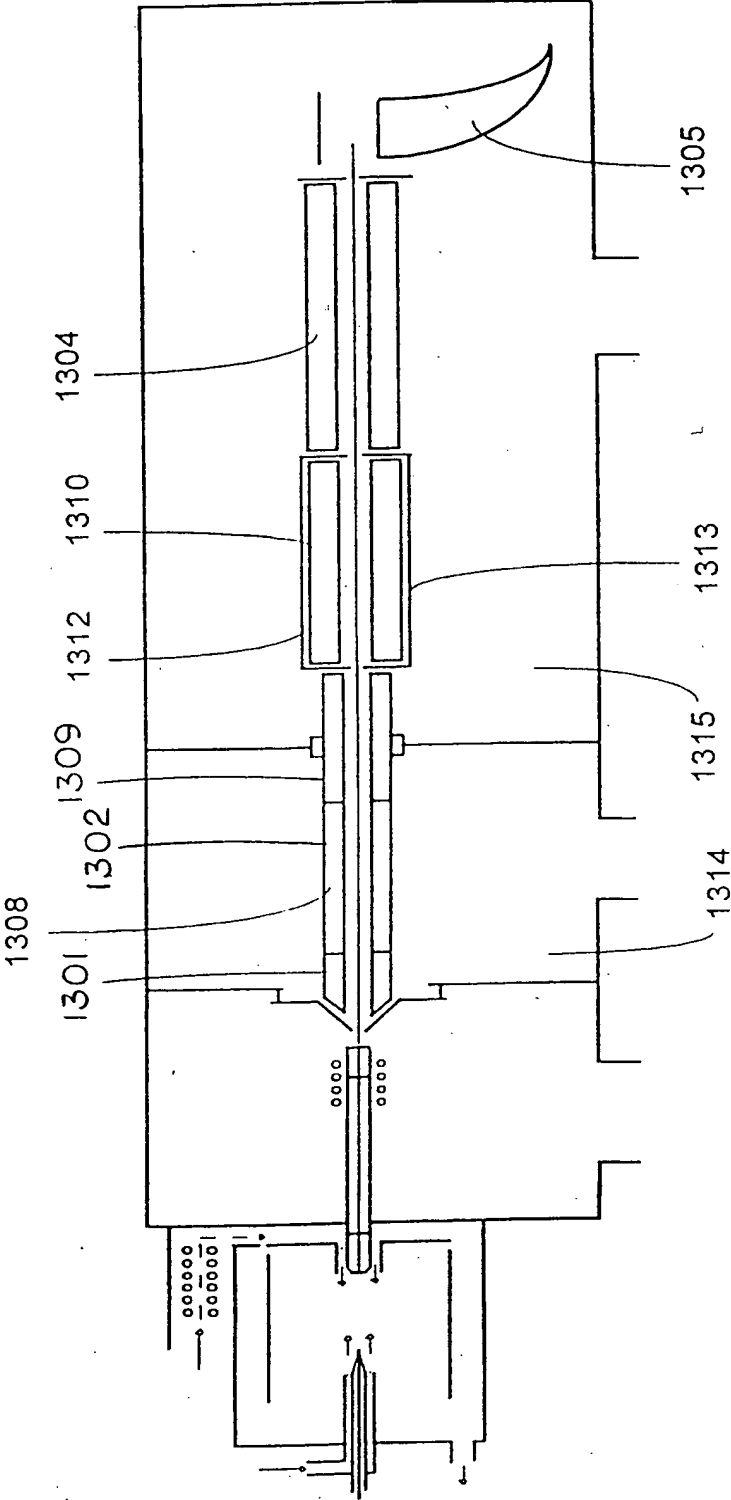


Figure 17

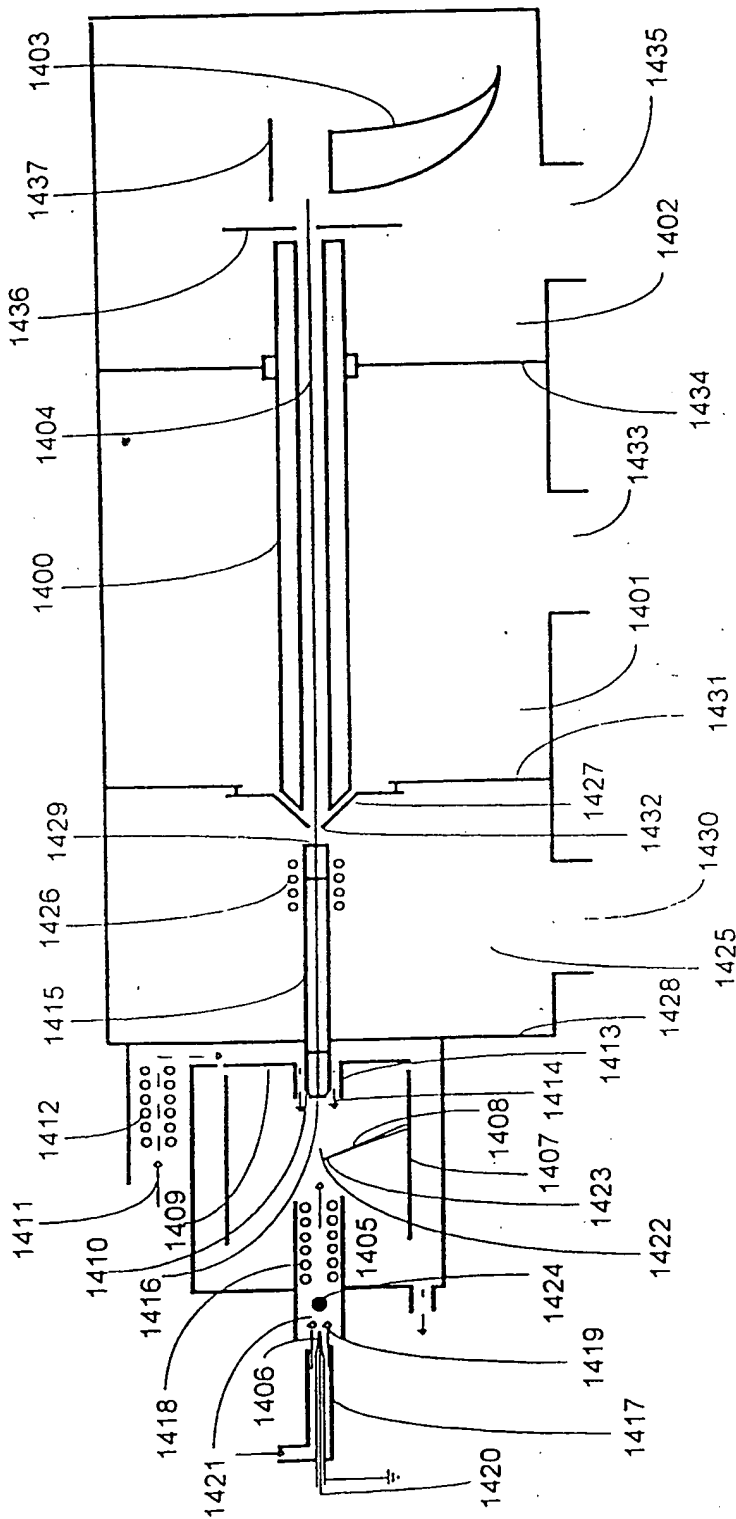


Figure 18



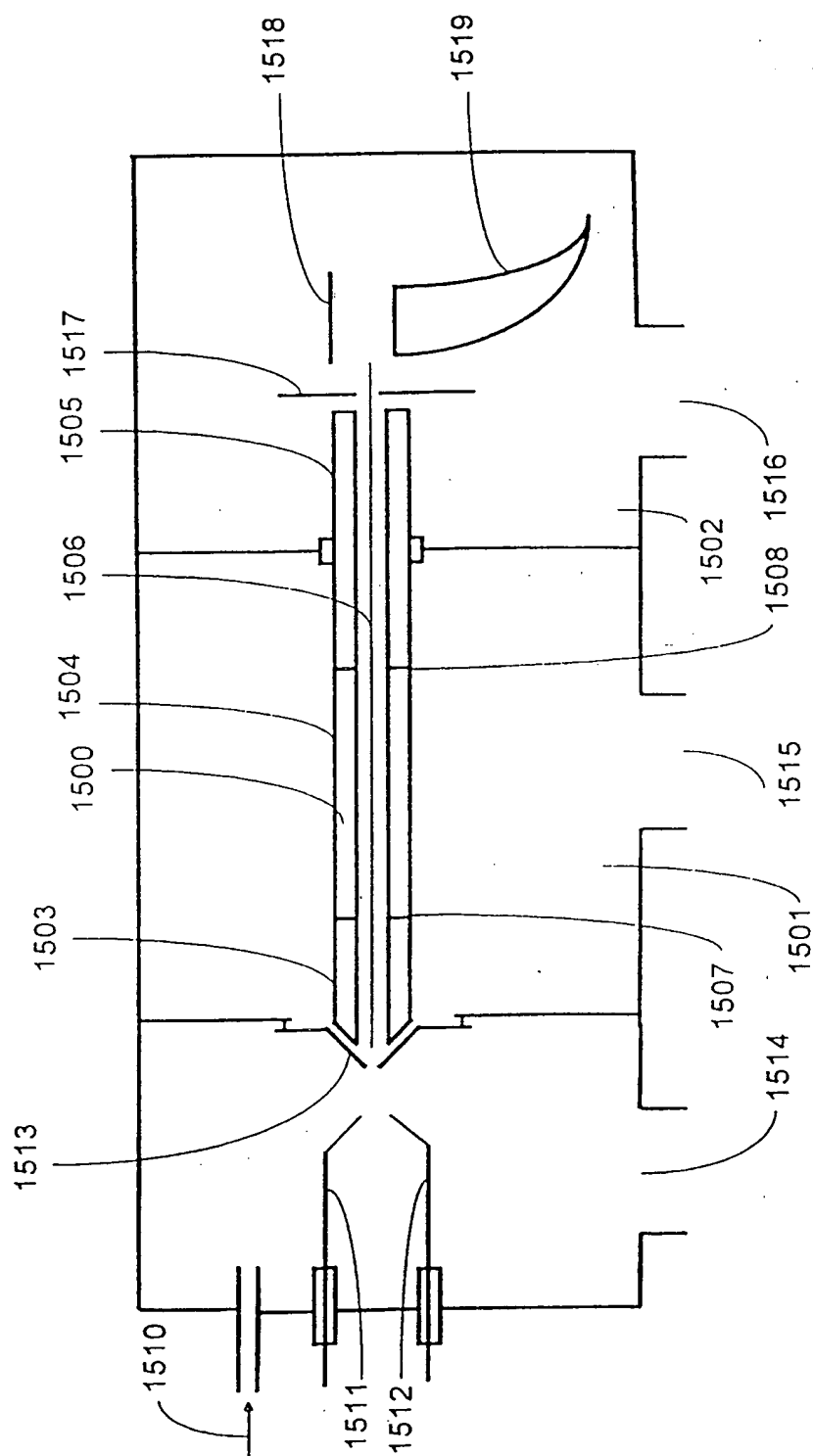


Figure 19

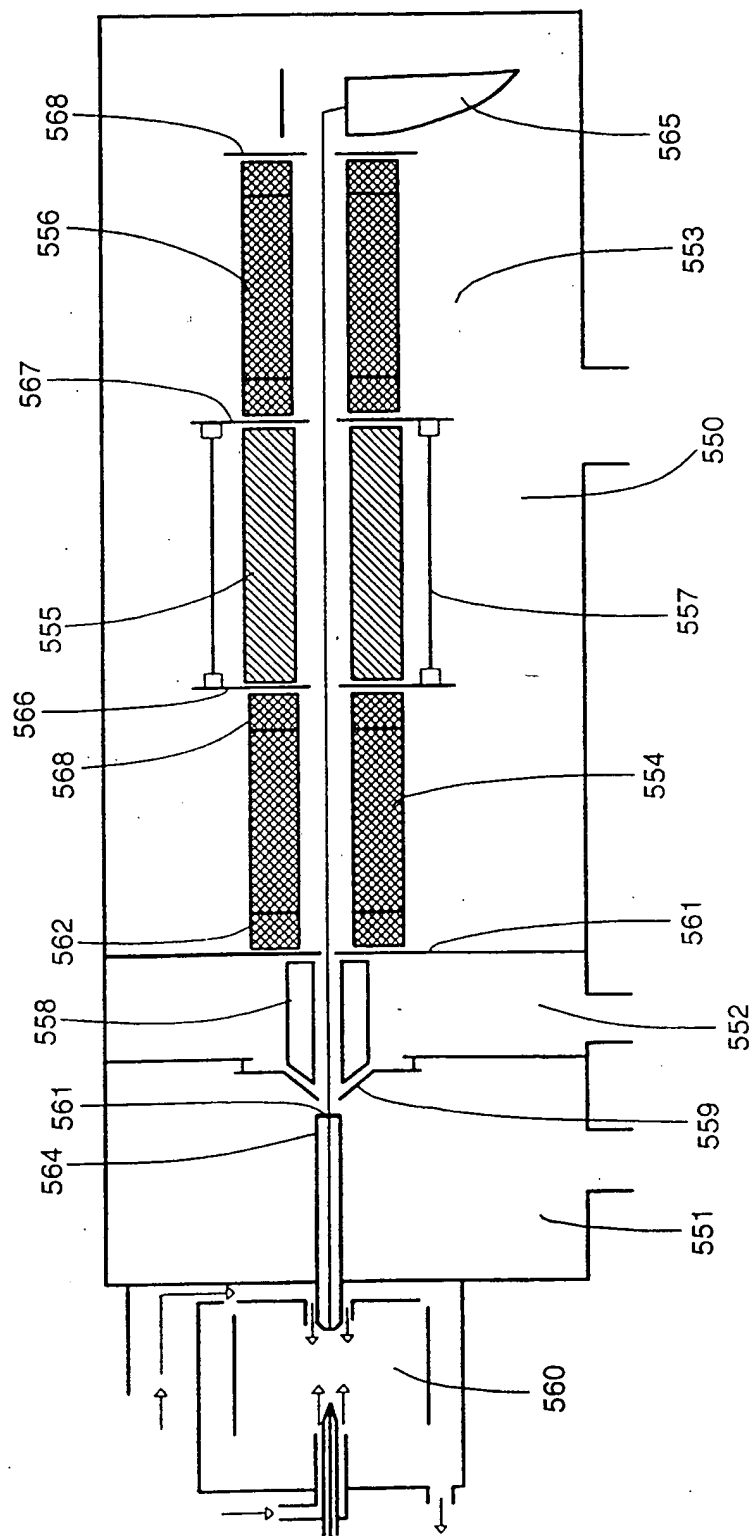


Figure 20

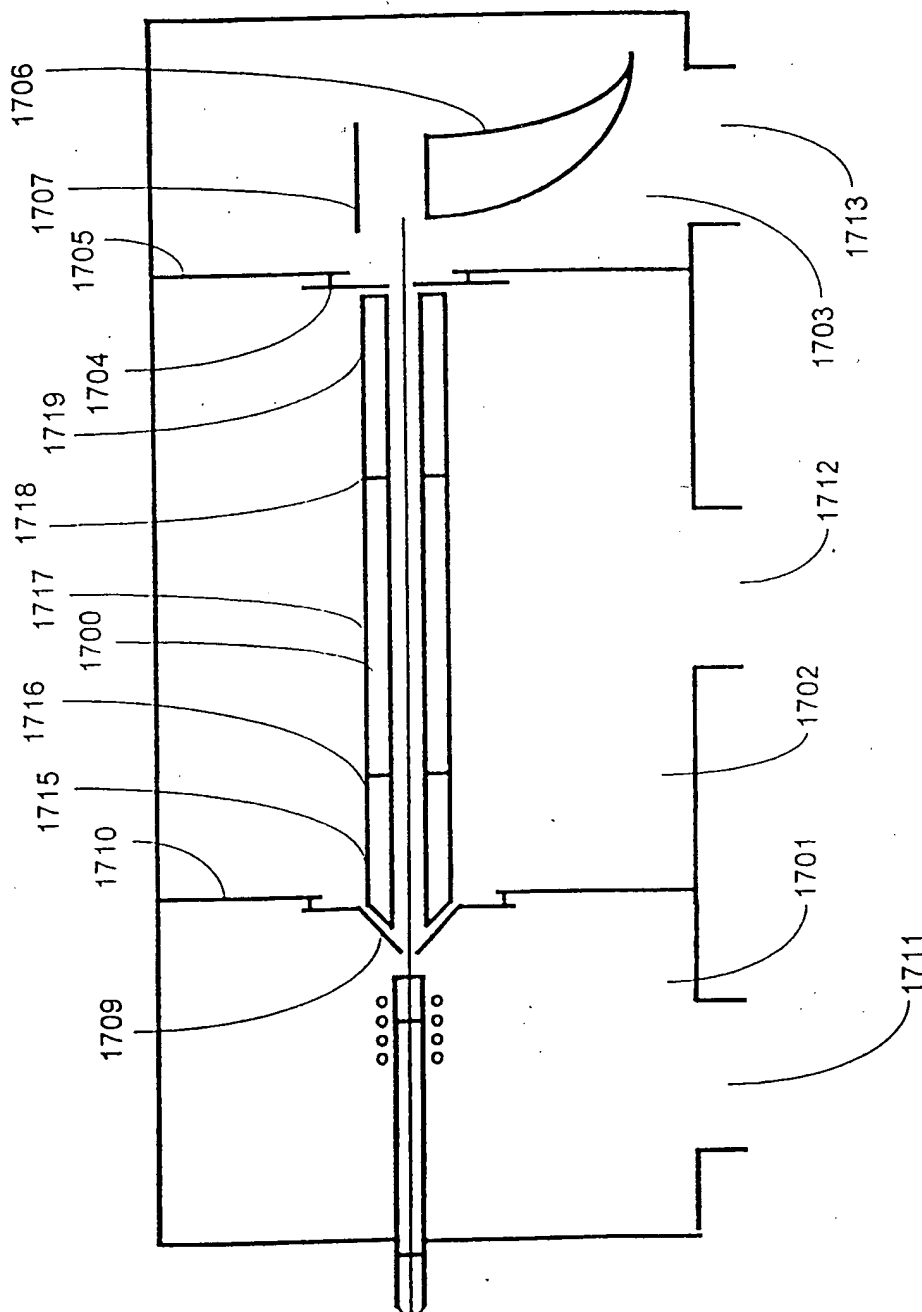


Figure 21

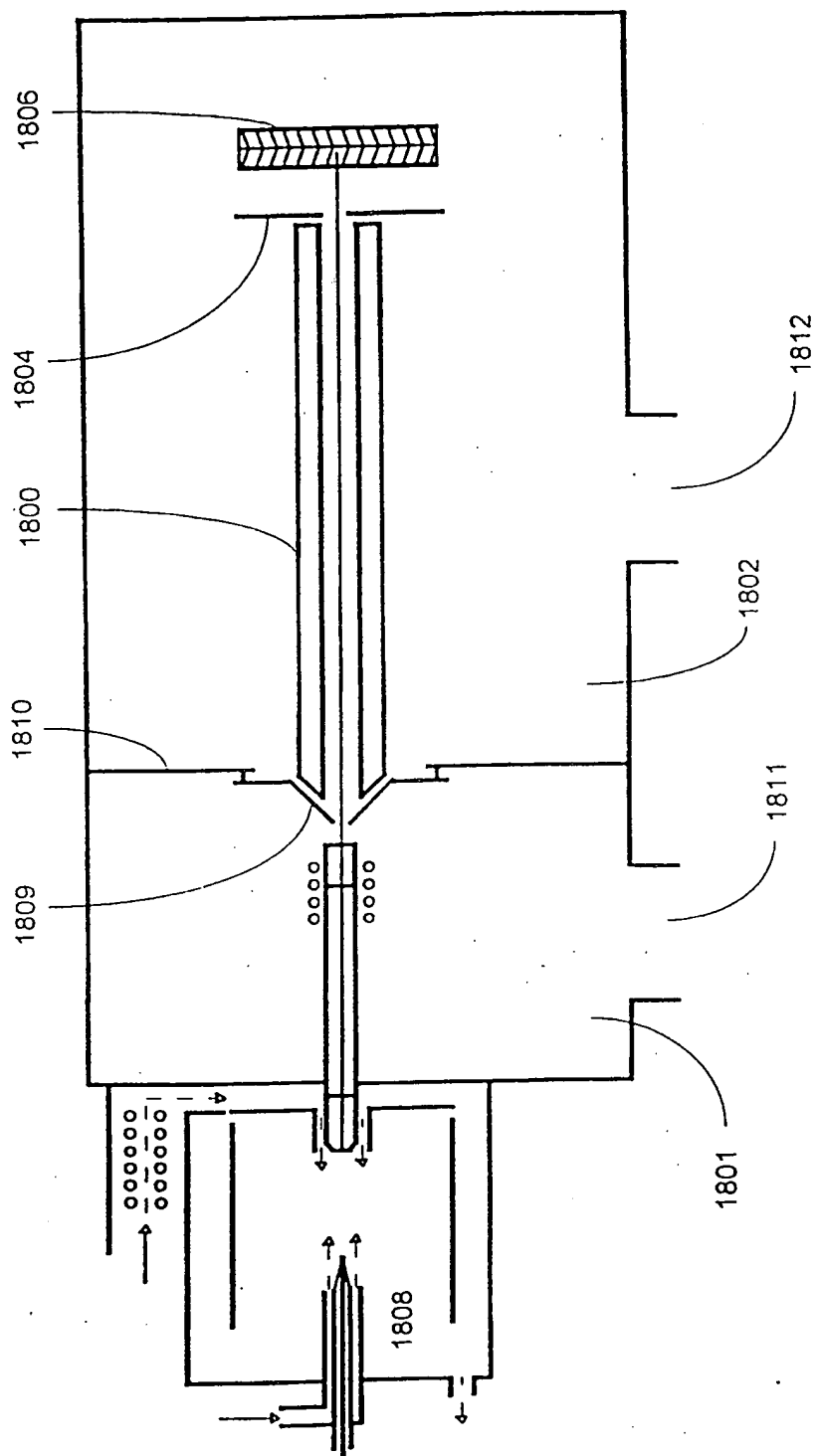


Figure 22

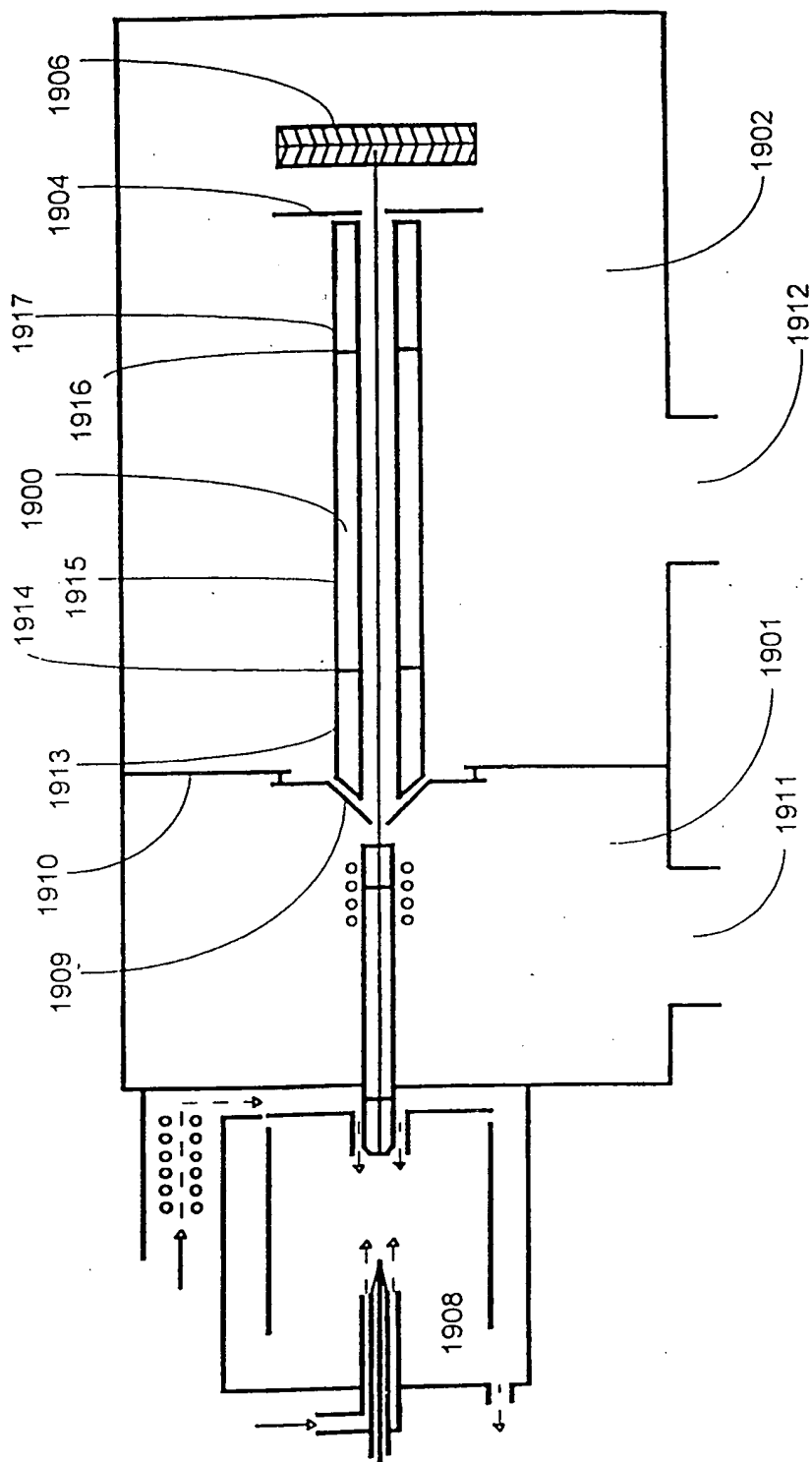


Figure 23

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/12169

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : H01J 49/42

US CL : 250/ 292

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 250/ 292

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
NONE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,652,427 A (WHITEHOUSE et al) 29 July 1997 (29-07-97), whole document, especially Figure 14 and col. 21, lines 41-64.	1-13 and 15-21
—		-----
Y		14 and 22-24
Y	EP 0,237,259 A2 (SYKA) 16 September 1987 (16-09-87), whole document.	14 and 22-24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

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